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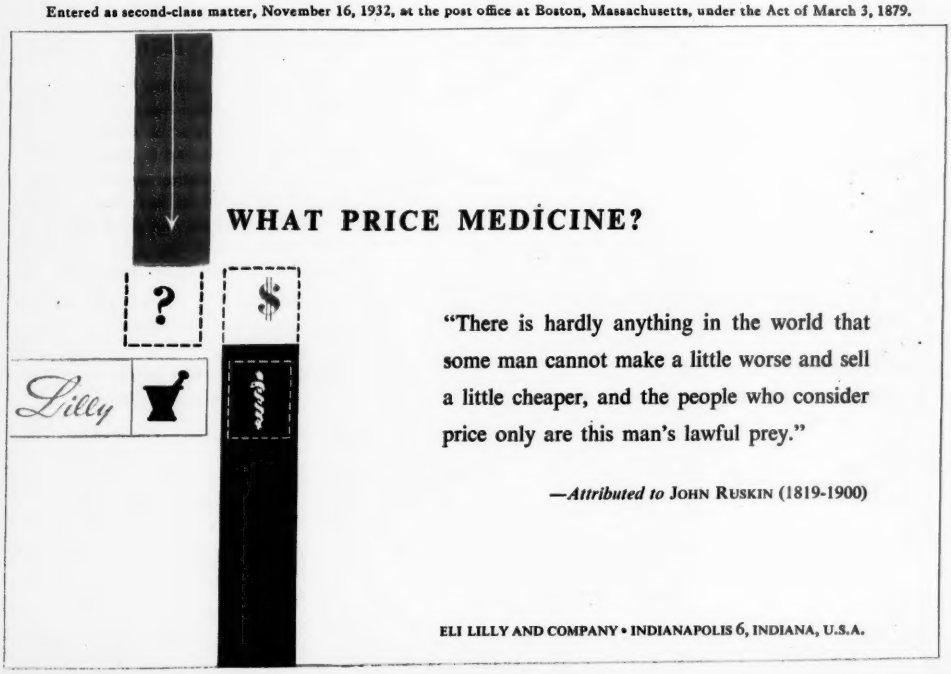
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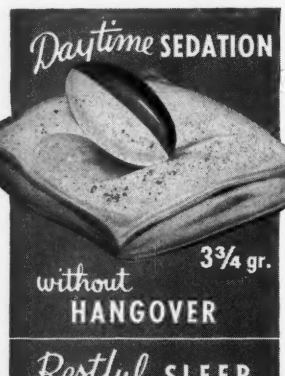

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MULTIPLE SCLEROSIS IN RURAL NORWAY*

Its Geographic and Occupational Incidence in Relation to Nutrition

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MONTREAL, CANADA, AND OSLO, NORWAY

THE investigation of the distribution of cases of multiple sclerosis in Switzerland between the years 1918 and 1922 seems to have established that the frequency of this disease can vary greatly in different geographic locations.[1] The subsequent studies by Gram[2] in Denmark and more recent investigations in the United States[3, 4] leave little doubt that these variations may be real and not due to technical errors in diagnosis, methods of collecting the data and so forth.

In another study, Swank[5] has suggested the possibility that these variations are related directly to the amount (and possibly the nature) of the fat consumption. It was pointed out, first, that the people of those countries considered to have a high incidence of multiple sclerosis consumed much fat, whereas those in low-incidence areas consumed little fat. Secondly, some of the variations in incidence during and following World War II might be explained by variations in the fat intake in that period. Thirdly, the variations of incidence in Switzerland might also correlate with varying fat consumption. In the high-incidence area of northern Switzerland the German language and culture prevail, and the diet probably contains much more fat than it does in the southern part of Switzerland, where the Italian language and customs prevail.

In order to obtain more data of a possibly more direct nature, a survey of the incidence of multiple sclerosis in all of Norway was undertaken. Norway was chosen because the mountains and fjords isolate the country into regions that of necessity tend to become economically dependent on their own environments. Since this survey revealed significant and consistent geographic differences, nutritional studies were undertaken in areas where the incidence of multiple sclerosis was low and in others where it was high. The combined studies are reported in this paper.

*Supported by a special grant from the Multiple Sclerosis Society of Canada.

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METHODS

To ascertain the relative incidences of multiple sclerosis, questionnaires were sent to all the hospitals and to many neurologic specialists in Norway. These sources were deemed adequate because of the high quality of neurologic and other medical diagnoses and care, their relative independence of both geography and economic level of the various parts of the country and the fact that cases in which diagnosis is uncertain are referred to the University Hospital (Rikshospitalet) in Oslo. Information was requested concerning the name, age, sex, domicile, occupation and year of the first multiple-sclerosis diagnosis of each patient in whom the diagnosis was first made between the years 1935 and 1948, inclusive. This period was chosen because it would give us some idea of the relative yearly incidence before, during and after World War II and because it was thought that a long period would yield a larger number of cases and therefore make more apparent any differences that might be present. The response to our questionnaires was approximately 80 per cent complete. No attempt was made to determine the prevalence rate of the disease (number of cases living), for reasons to be discussed later.

Nutritional surveys were performed in 7 rural districts. These districts were chosen in an attempt to avoid unusual and difficult circumstances. In each district a number of families were studied by methods used before by Strøm.[6] All the food that came into the house was measured or weighed during one week and all food stocks were checked before and at the end of this week. The daily intake per man unit of all foods was then calculated, and finally the number of grams of protein, fat and carbohydrate were determined according to the Cathcart scale. Four other coastal districts studied between 1928 and 1940 by other investigators are included in our consideration of the nutrition along the coast; the results of these studies are included in Table 5.

Results

Incidence of Multiple Sclerosis

A total of 1161 cases of multiple sclerosis was reported for an average total population of 3,123,368 (1946 Census). This made an incidence rate of newly diagnosed cases during the fourteen-year period 1935 to 1948 of 2.7 per 100,000 per year for all of Norway. The number of new cases diagnosed each of these years is shown in Table 2. This suggests a fairly uniform yearly rate before and during the war, with an increase in the yearly rate for 1946 and 1947. This indicates that the postwar increase of cases of multiple sclerosis at the Rikshospital reported previously[5] reflected a national increase, since this hospital receives patients from all of Norway. The 1939 increase noted in the same hospital was evidently not accompanied by an increase of the total number of cases in Norway and probably indicated either an unusual migration of cases to the Rikshospital for diagnosis and treatment or a purely local increase. The ratio of female to male cases during the fourteen-year period was approximately 1:1 (575 male and 586 female). The rural population in Norway was 2,246,609, with 819 cases of multiple sclerosis. This gives an incidence rate of 2.6 per 100,000 per year. For the urban population of 876,759 the 338 cases give an incidence rate of 2.8 per 100,000 per year. The ratio of urban to rural populations (2.8:2.6) is not helpful in our analysis, as will be shown later.

To obtain an idea of the distribution of these cases and draw some conclusions concerning the lives and habits of the people in regions with varying incidences of the disease, both the geographic distribution and the distribution by occupations have been studied.

The geographic incidence of multiple sclerosis. The geographic distribution of the cases in rural areas only is shown in Figure 1, and all the figures involving rural populations are shown in Table 1. The numbers on the map in Figure 1 indicate the number of rural cases per year per 100,000 rural population. It appears that despite the small number of cases and the thinly populated areas involved a relatively low incidence of multiple sclerosis persisted along almost the entire coast of Norway. One small coastal area in Rogaland province,* centering on the districts Helleland, Eigersund and Varhaug (opposite the X in Figure 1), exhibited a high incidence of multiple sclerosis, but the numbers of cases and total population were small (population 9375; 9 cases; rate approximately 6.4/100,000 per year) and therefore of questionable significance. In part of the province of Vest-Agder a high rate of multiple sclerosis also extended to the coast. The remaining coastal areas were surprisingly consistent in their rates, as indicated in Figure 1.

The rural areas of high incidence of multiple sclerosis were located in southern Norway (the eastern part of Ostfold, Akershus, Buskerud, the inland part of Telemark, the western part of Aust-Agder and the eastern part of Vest-Agder),Opland and Hedmark and the inland part of Sør- and Nord-Trøndelag. A very small area inland from the coastal town of Bodø in the province of Nordland also exhibited a high incidence of this disease, but because of the small number of cases involved

Table 1. *Rural Population Figures, Number of Cases of Multiple Sclerosis and Incidence Figures for All Areas Appearing in Figure 1.*

Province		Rural Population 1946	No. of Cases of Multiple Sclerosis 1935–1948	Yearly Rate Per 100,000 Population
Østfold	Coastal	81,750	11	0.9
	Inland	40,905	27	4.7
	Entire province	122,655	38	2.2
Akershus	Coastal	199,283	74	2.6
	Inland	94,639	61	4.6
	Entire province	293,922	135	3.3
Hedmark	Near Hamar	53,013	7	0.9
	Rest of Hedmark	102,298	47	3.3
	Entire province	155,311	54	2.5
Opland	Entire province	141,694	76	3.9
Buskerud	Entire province	110,199	78	5.1
Vestfold	Entire province	102,040	54	3.8
Telemark	Coastal	17,467	3	1.2
	Inland	73,778	56	5.4
	Entire province	91,245	59	4.6
Aust-Agder	Coastal	47,113	8	1.2
	Inland	8,498	8	6.7
	Entire province	55,611	16	2.1
Vest-Agder	Eastern part	35,226	29	5.9
	Western part	25,467	4	1.1
	Entire province	60,693	33	3.9
Rogaland	Entire province	121,142	28	1.6
Hordaland	Entire province	186,954	6	0.2
Sogn og Fjordane	Entire province	94,305	8	0.6
Møre og Romsdal	Entire province	146,572	35	1.7
Sør Trøndelag	Coastal	36,374	15	2.9
	Inland	99,333	75	5.4
	Entire province	135,707	90	4.7
Nord Trøndelag	Coastal	17,908	2	0.8
	Inland	78,759	43	3.9
	Entire province	96,667	45	3.4
Nordland	Fjord part	16,800	14	5.9
	Rest of Nordland	170,876	32	1.4
	Entire province	187,676	46	1.8
Troms	Entire province	98,159	15	1.1
Finmark	Entire province	46,628	3	0.4

Table 2. *The Number of New Cases of Multiple Sclerosis Diagnosed Yearly for All of Norway and by the Rikshospital, Oslo.*

Year	New Cases in All of Norway	New Admissions to Rikshospitalet, Oslo
1935	83	
1936	78	
1937	76	27
1938	77	21
1939	89	52
1940	70	30
1941	78	23
1942	74	26
1943	69	23
1944	81	26
1945	88	31
1946	113	29
1947	101	55
1948	83	65

*The term province is used throughout to replace the correct Norwegian term "fylke." The provinces are the large subdivisions of Norway that are labeled in Figure 1. The provinces ("fylke") are subdivided into districts (Table 4).

(population 16,800; 14 cases; rate 5.9/100,000 per year) this may not be significant. In Opland the northern mountainous districts (Skjaak, Lom, Vaagaa and Heidal) exhibited higher multiple-sclerosis rates than were recorded for the entire province. In the province of Hedmark, the most northerly and mountainous districts (centering on the districts Folldal, Kvikne and Solør) also exhibited higher rates. In Hedmark the area around Hamar exhibited a very low incidence of multiple sclerosis (see Figure 1; 0.9/100,000 per year). The reason for this is not apparent.

If one considers only the more typical coastal "fishing" and inland "farming" areas, leaving out Vest-Agder, where the division was not on a coastal-inland basis, the relation shown in Table 3 is to be noted. The variation from these averages is surprisingly small.

In the low-incidence coastal areas, fishing is the only or chief occupation. In addition to fishing, most of the inhabitants in this area either have a very small plot of land, on which they raise their own potatoes and a few vegetables and some livestock, or engage in a part-time craft. According to the 1930 census this coastal area of low incidence of multiple sclerosis also corresponded closely with the lowest-income areas of Norway.

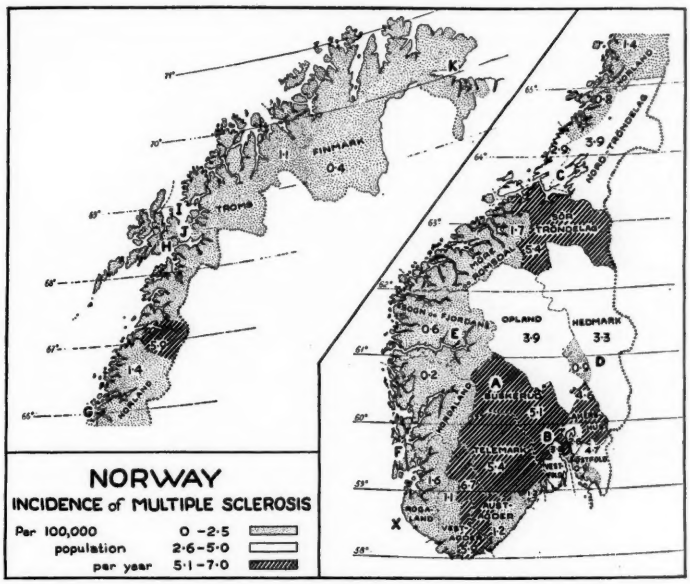

FIGURE 1. *Geographic Distribution in Rural Norway of Cases of Multiple Sclerosis Diagnosed 1935 to 1948.*

The figures on the map indicate average yearly incidence of the disease among the rural population; the letters A to K indicate where dietary surveys were performed.

TABLE 3. *Average Incidence of Multiple Sclerosis Per 100,000 Inhabitants Per Year in Coastal and Inland Areas.*

	POPULATION	CASES	ANNUAL INCIDENCE
Coastal	1,082,048	180	1.2
Inland	905,156	532	4.1

In the inland high-incidence areas farming and dairying predominate. Lumbering, small industry and crafts are also scattered throughout these areas; hence the economy is mixed, as it is along the coast.

The incidence of cases of multiple sclerosis within the farming and dairy areas, in addition to being high, also varied markedly from one section to another. Many of the *very high*-incidence areas (5 to 7/100,000 per year) in Telemark, parts of Buskerud, Aust-Agder, the southern part of Sør-Trøndelag and the inland area near Bodø in Nordland are relatively isolated by mountains and fjords or by great distances. The somewhat lower-incidence areas of Opland, Hedmark, Akershus, Vestfold and Nord-Trøndelag include some of the best non-mountainous farming areas, much of which have a ready access to markets and centers of populations. These are the grain and potato as well as dairy regions of Norway.

The urban incidence rate was very high (7 to 11/100,000 per year) in Sandefjord, Drammen and Kongsberg. These towns are very prosperous. In all other urban areas the incidence did not vary

greatly from the surrounding rural area. For example, the incidence within Oslo was almost identical to the rate of the immediately surrounding rural districts.

The occupational incidence of multiple sclerosis. Because the farming in Norway is frequently mixed with fishing, lumbering and small industry and because the borders between high- and low-incidence areas are to some extent arbitrary and not distinct, it has been necessary to carry our studies further and correlate the incidence of multiple sclerosis with the occupation predominating in the districts and also the provinces. This correlation may refer more closely to the habits of living and eating of the populations under consideration. The records from the census of population in 1946 give the percentage of the population in each district that gains its principal income from agriculture and forestry, fisheries or industry and handicraft. From this same source can be obtained the average amount of taxable income per individual.

TABLE 4. *Number of Cases of Multiple Sclerosis Per 100,000 Population Per Year and Taxable Income Per Person in 1947.*

PROVINCE	TAXABLE INCOME PER PERSON IN 1947	FARMING DISTRICTS	NON-FARMING DISTRICTS	TOTAL
Østfold	1945	3.21	1.93	2.21
Akershus	2247	4.36	3.14	3.28
Hedmark	1429	2.57	2.07	2.50
Opland	1348	3.93	3.50	3.78
Buskerud	1872	*5.93*	4.78	*5.07*
Vestfold	2024	2.50	3.93	3.78
Telemark	1942	*6.64*	3.21	*4.64*
Aust-Agder	1307	2.71	1.79	2.07
Vest-Agder	1374	*5.50*	3.14	3.86
Rogaland	1584	1.86	1.57	1.64
Hordaland	1596	(0.93)	(0.14)	(0.21)
Sogn og Fjordane	1186	(0.64)	(0.57)	(0.57)
Møre og Romsdal	1254	3.71	1.21	1.71
Sør-Trøndelag	1381	*4.93*	4.64	*4.71*
Nord-Trøndelag	1263	4.00	2.36	3.36
Nordland	1034	3.36	1.64	1.79
Troms	958	(1.21)	(1.07)	(1.07)
Finmark	1352	—	(0.43)	(0.43)

On the basis of this information the districts in each province have been divided into two groups: those districts where 50 per cent or more of the population gain their living through agriculture and forestry (farming districts) and those where 50 per cent or more of the population gain their chief income from nonfarming occupations (fisheries, industries and so forth). In Table 4 these data have been summarized; it shows the average incidence of multiple sclerosis per 100,000 inhabitants per year reported during the 1935–to–1948 period, in the farming districts and in nonfarming districts for each province.

It is evident that the incidence of multiple sclerosis in the typical farming districts, when singled out in this way, is significantly higher than that in the nonfarming areas (Table 4). This tendency is present in the coastal as well as in the inland provinces. The only exception is Vestfold, where the highest frequency is observed in the non-farming districts. The reason for this is not apparent, but it might be pointed out that the nonfarming occupations in Vestfold include shipping and whaling, both of which industries are and have been very prosperous. The provinces Hordaland and Sogn og Fjordane have so few cases of multiple sclerosis that the chance distribution of these cases between farming and nonfarming occupations could be misleading. The incidence rates in the provinces Troms and Finmark should also be considered with reservations for this same reason.

Great variations are to be observed in the incidence rates of the different farming districts. In Buskerud and Telemark the incidence of multiple sclerosis is very high, whereas in Ostfold and Hedmark, where the occupational structure of the population is similar, the incidence is lower. Equally noteworthy is the high rate of the disease in the farming districts of Vest-Agder, compared with the neighboring provinces Aust-Agder and Rogaland. Some of the best farming districts of Norway with a high production of dairy products are situated in parts of Rogaland. The production of dairy products is greater only in Opland and Hedmark; in these provinces the incidence of multiple sclerosis is lower than in other farming districts in Buskerud, Telemark, Vest-Agder and Sør-Trøndelag. As will be seen in Table 4, the frequency of multiple sclerosis in the farming districts of Møre og Romsdal, Nord-Trøndelag and Nordland is the same as in the farming districts in the southeast part of Norway.

If we consider the districts engaged primarily in nonfarming occupations we find the rate of multiple sclerosis generally lower than for farming districts of the same province. The rates in the nonfarming districts vary between 4.78 per 100,000 inhabitants per year in Buskerud to 1.21 per 100,000 per year in Møre og Romsdal, but no consistent differences are present. We find the nonfarming rate about the same in the provinces Ostfold, Hedmark, Aust-Agder, Rogaland, Nord-Trøndelag and Nordland and also the same in the provinces Vest-Agder, Telemark, Opland and Akershus.

Nutritional Survey

The diets of seven rural districts (see below, A to G) were studied between October, 1950, and March, 1951. To these can be added similar studies (see below, H to K) of 2 fishing districts, Lødingen and Bjarkøy, by Evang, Galtung-Hansen, Lid and Lund[7, 8] in 1935 to 1937, a study of the fishing district Skaanland by Storstein[9] in 1938, and a survey of other fishing districts centering on Vadsø in northern Finmark by Kloster,[10] 1928–1930. These earlier studies are of value, since changes in the diet appear to have occurred since 1945 in the fishing districts. The rural districts studied are characterized in a general way as follows:

A. Hol is a rather prosperous farming and rural industrial district with a population of 3479 and 3 reported cases of multiple sclerosis. The diet of 26 families was studied.

B. Eiker is a prosperous farming, lumbering and industrial district with a population of 19,226 and 12 reported cases of multiple sclerosis. The diet of 22 families was studied.

C. Leksvik is a farming district with a population of 3267 and 3 reported cases of multiple sclerosis. The diet of 21 families was studied.

D. Elverum is a more prosperous farming and lumbering district with a population of 11,909 and 9 reported cases of multiple sclerosis. The diet of 22 families was studied.

E. Sogndal is a mixed district with a population of 3643 and no reported cases of multiple sclerosis. About half the population are prosperous farmers; only these were included in the dietary survey. The other half are industrial workers, much less well off, who live in the village. The diet of 23 farming families was studied.

F. Sveio is a nonprosperous coastal farming and fishing area with a population of 1943 and no reported cases of multiple sclerosis. The diet of 21 families was studied.

G. Herøy is a poor fishing district with a population of 2823 and no reported cases of multiple sclerosis. The diet of 23 families was studied.

H. Lødingen is a fishing district with a population of 3939 and no reported cases of multiple sclerosis. The diet of 22 families was studied by Evang and others, 1935–1937.

I. Bjarkøy is a fishing district with a population of 1999 and no reported cases of multiple sclerosis. The diet of 5 families was studied by Evang and others, 1935–1937.

J. Skaanland is a poor fishing district with a population of 2729 and no reported cases of multiple sclerosis. The diet of 9 Lapland families was studied by Storstein[9] in 1938.

K. Vadsø is a fishing district with a population of about 4650 and no reported cases of multiple sclerosis. Kloster[10] in 1931 studied many families in this very homogeneous settlement and estimated the average daily dietary intake of the inhabitants.

The geographic position of each of these districts is indicated in Figure 1 by the letter before each of these districts; the results of the survey are tabulated in Table 5.

In the seven districts studied during 1950–1951, the total intake of fat was high and of about the same magnitude. There were marked qualitative differences, however. The butterfat intake was much higher in the farming districts than in the two coastal fishing districts (Sveio and Herøy). The intake of margarine maintained an approximate reciprocal relation to the intake of butterfat. This relation was also noted by the margarine manufacturers, who informed us that the use of margarine was greatest in the fishing districts and least in the farming districts. Consistent and significant differences in other types of fat consumed were not noted in our 1950–1951 survey. The high intake of fish fat in Sogndal was seasonal and was due to the consumption of large quantities of fresh herring at that time.

In the coastal fishing districts the intake of fish protein was very high; in the inland fjord districts (Leksvik and Sogndal) it was moderately high. In general the intake of protein was adequate.

The earlier studies of Evang and his co-workers[7, 8] Storstein[9] and Kloster[10] indicated a much lower butter and animal fat and lower total fat intake in the fishing districts prior to our 1950–1951 studies. Moreover, in the northern part of the province of Finmark the intake of fish-liver oil was remarkably high.[10]

In all likelihood the increase in the total fat and particularly in the butter and animal fat in the diet along the coast occurred after 1945, when the Ger-

TABLE 5. *Amount of Chief Foodstuffs (in Gm.) Consumed in Each District.*

	Present Studies (1950–1951)*							Earlier Studies (1931–1938)			
	A. HOL	B. EIKER	C. LEKSVIK	D. ELVERUM	E. SOGNDAL	F. SVEIO	G. HERØY	H. LØDINGEN	I. BJARKØY	J. SKAANLAND	K. VADSØ
Population	3,479	19,226	3,267	11,909	3,643	1,943	2,823	3,939	1,999	2,729	4,650
No. of cases of multiple sclerosis	3	12	3	9	0	0	0	0	0	0	0
No. of families studied	26	22	21	22	23	21	23	22	5	9	—
Milk, butter, cream, cheese	88.44	70.01	69.53	65.73	78.87	46.33	39.79	22.21	27.57	24.08	18.00
Animal fat	20.06	34.60	35.49	30.96	40.03	32.97	30.97	6.33	8.93	12.84	
Margarine fat	28.08	50.63	43.35	68.64	31.64	60.84	86.23	50.18	54.20	48.13	59.20
Fish fat and cod liver oil	3.74	3.08	4.61	5.00	8.37	4.44	11.36	2.81	2.37	6.11	50.60
Vegetable fat	7.50	7.69	8.83	8.05	8.49	9.07	10.16	9.40	7.37	12.27	5.30
Total fat	147.82	166.01	161.81	178.38	167.40	153.65	178.51	90.93	100.44	103.43	133.10
Animal protein	59.93	65.26	59.22	75.38	60.02	59.02	48.12	26.80	27.80	46.22	
Fish protein	12.60	9.53	18.24	7.72	20.71	26.63	32.82	30.90	26.80	26.88	115.10
Vegetable protein	40.45	43.11	51.49	44.17	42.18	47.20	44.27	56.10	47.30	75.10	64.00
Total protein	112.98	117.90	128.95	127.27	122.91	132.85	125.21	113.80	101.10	148.20	179.10
Carbohydrate†	342.2	361.4	403.8	376.0	354.8	374.5	364.3				541.5
Calories†	2883.2	3116.7	3289.9	3299.2	3125.1	3125.4	3248.4				

*These figures are gross values and do not account for waste that will figure at approximately 10 per cent to 15 per cent.
†Net figures calculated with 15 per cent for waste.

man occupation ended and the effective income of the coastal fishermen increased. Prior to the war the fisherman had lived largely off their small plots of land and the sea, and they had "ready cash" only during the fishing season in the spring. Since the war these same fishermen have had ready cash throughout the year. It can be said with reasonable certainty that during the period of the multiple-sclerosis-incidence survey (1935–1948) the total fat and butterfat intakes were between the figures determined by the earlier investigators and those obtained by ourselves for 1950–1951. We are also reasonably certain that the values for fat found by ourselves in 1950–1951 are higher than those that existed during the period of multiple-sclerosis survey. Probably the correct intake during most of the period of survey was approximately the same as was found by the earlier investigators. In any event it is clear that the butter and animal fat intake in coastal fishing districts was much lower (possibly as much as 65 per cent) and the total fat intake in the coastal regions somewhat lower (possibly as much as 35 per cent) than in the farming districts during the period of multiple-sclerosis-survey from 1935 to 1948. There is no reason to suspect that a change has occurred in the diet of the farmers since the war.

Discussion

The incidence of multiple sclerosis in rural districts of Norway has shown striking geographic differences, amounting to an average inland farming to coastal fishing district ratio of about 4.1 to 1.2. Such a striking geographic difference has not been shown by recent surveys, possibly because the prevalence rather than the incidence of the disease was determined. Prevalence figures may not indicate true differences in incidence, since they are influenced by the severity and hence the duration of the disease. Since it is likely that the disease would progress more rapidly and have a shorter duration in areas where its incidence is highest (causative agents are more prevalent), an incidence difference of 4 to 1 could conceivably give a prevalence ratio of 2 to 1 if the average duration of the disease were twice as long in the area of lowest incidence. Ipsen[11] has recently discussed this problem.

The impression gained from our geographic survey that a high incidence of multiple sclerosis is associated in Norway with farming and with dairying is reinforced by the results of our occupational study. In all provinces but one, the incidence of multiple sclerosis in districts in which farming predominated was significantly higher than in districts in which nonfarming occupations predominated. It seems unlikely, therefore, that incomplete diagnoses and reporting of cases can account for the geographic difference, although from a statistical point of view our material is small and may not be completely representative.* Gram [2] also found that in Denmark the prevalence of disabling multiple sclerosis was greater among farmers (51/100,000) than among city dwellers (37/100,000).

The reason for the relatively high incidence rates that we have noted for multiple sclerosis among the rural population in farming districts may be the environmental or dietary habits of these people. In all likelihood the farmers and their families have eating habits that differ from the rest of the population; in particular, their intake of butter and animal fats is probably greater. Although supportive of this point of view, our own nutritional material is not statistically conclusive since it samples only a small material and does not consider at all many groups of people and many areas.

If it is true that the intake of fat is the factor that determines the incidence of multiple sclerosis, we are left with the problem of why such marked variations were observed in the farming districts. It is likely that those farmers with well developed and accessible markets will have a tendency to sell relatively more of their expensive fat-containing produce such as dairy products, pork and beef and will consume relatively more of the cheaper foods such as margarine and cereals. It has been shown by a League of Nations survey[12] that the less prosperous farmers behave similarly. On the other hand, the relatively isolated farmers and also the more prosperous ones will have a tendency to consume more of their fat-containing products. These factors, plus the availability of fats and the customs of the people, will determine the fat intake of the people and possibly the incidence of multiple sclerosis.

The factors that determine the consumption of fat may explain the very low incidence of multiple sclerosis in Hordaland and Sogn og Fjordane, despite the fact that many of the people in these provinces support themselves largely by farming. It is also possible that our statistical material from these two provinces is less representative than that from others because of the possibility that a relatively smaller number of their cases were sent to hospitals. This cannot be determined, although it is of interest that the officially-listed numbers of deaths from unknown and ill-defined conditions are higher in Hordaland and Sogn og Fjordane than elsewhere in the south of Norway. These two provinces are very large, and their populations are scattered. This might tend to lessen the efficiency of medical care and hence decrease the number of cases reported. Any significant change in this direction seems unlikely, however, in view of the fact that the incidence rate of multiple sclerosis in the city of Bergen (in Hordaland) was still low though slightly higher than for the entire province. This city, with a population

*Schnitler has recently reported in discussion a very low incidence of multiple sclerosis along the coast of Trøndelag and Møre and a much higher incidence in more inland areas (*Report on the Eleventh Congress of Scandinavian Neurologists*, Copenhagen, 1950, see discussion, p. 45). This same material was included in our geographic survey, which was reported briefly in the *Transactions of the American Neurological Association* in 1950.

of 108,933, has adequate medical care and reported 18 cases of multiple sclerosis for an incidence of 1.2/100,000 inhabitants per year.

Our nutritional figures covered short periods and conceivably could be influenced by seasonal dietary changes. One such change was observed in Sogndal, where the fresh-herring intake was very high. This did not disturb the basic pattern of food consumption, however. To avoid significant seasonal variations, the two holiday seasons during which the intake of fat traditionally increases in Norway (Christmas and Easter) were not included in our studies in any rural district.

With the exception of the fjord district of Sogndal, the incidence of multiple sclerosis in the districts that we studied in Norway varied directly with the amount of the butter and animal fat intake. The total fat intake in the low-incidence coastal areas was also lower than in the higher-incidence areas, but this difference was less striking. Sogndal may be a special case, since it appears to be located in a low-incidence area, yet its people seem to be high butter and animal fat consumers. This was the only mixed district that we studied. It is small, and only part of its population is engaged in farming; the rest work in the woolen industry. Our survey, unfortunately, included only the farmers and therefore is probably misleading. Furthermore, Sogndal is far from the coast and in a mountainous and very thinly populated part of Norway. It has been included in the low-incidence area because of the natural province boundaries. If the populations were greater this area might have had a high incidence of multiple sclerosis and consequently be included with the provinces farther inland. If, as suggested previously,[5] a high intake of fat increases the incidence of multiple sclerosis by precipitating the disease in susceptible persons, then the present study would indicate that *butter fat is a more effective precipitating factor than fish-liver oil, Norwegian margarine or vegetable oil.*

Unfortunately, one cannot regard these relations as established. The number of cases of multiple sclerosis, the total populations considered and the number of districts in which nutritional studies were made are relatively small. These undesirable features are difficult to alter, however, because we are dealing with an uncommon disease and because the difficulties of conducting this type of survey in more populated regions would be enormous.

In support of our figures, one must not overlook the following points. First, in Norway we are dealing with a fairly uniform and stable population. Secondly, the country is divided by deep fjords and high mountains into relatively inaccessible areas, in each of which the rural populations depend for their living largely on their environment. As a result, a simple and homogeneous pattern of life has developed that is suited to each of these areas. Thirdly, medicine in general, — and neurologic diagnosis in particular, — is uniform and of high standard. More than half the patients we studied were admitted to the clinic of Professor Monrad-Krohn at the Rikshospital in Oslo, and most, if not all, of the remaining patients were seen by neurologists trained in this same clinic. It would have been difficult to attain more uniform diagnostic standards during the period of our survey (1935–1948). Fourthly, although Norway was occupied by the Germans during the middle period of our survey, the hospitals and medical services remained intact and functioned without significant alteration. Furthermore, the dietary restrictions that were noted in the cities[6] were much less evident (if present) in the rural areas. Finally, the low incidence of multiple sclerosis in the coastal fishing area and the high incidence in the inland farming and dairy areas have been remarkably consistent. The variations from this rule have been insignificant when compared with the over-all picture.

There is little but suggestive evidence in the literature to support the hypothesis that a high fat intake may cause a high incidence of multiple sclerosis. In a previous study[5] it was pointed out that in general the fat intake was low (60 gm. daily or less) in countries thought to have a low incidence of multiple sclerosis. Very little milk, and animal fat was available for consumption in most of these countries, and the incidence of multiple sclerosis in those with the lowest milk intake (southern Italy, Turkey, China and Japan) was possibly lower than we observed along the coast of Norway. On the other hand, milk and animal fats were a much larger source of the total fat intake in those countries where the incidence of multiple sclerosis is thought to be high. The statements relative to the fat intake are based on figures published by the U.N.F.A.O.[13] The apparent marked increase in the number of disabling cases of multiple sclerosis among the rural people in Denmark during the war[5] would also support our thesis that butter and animal fat are very important precipitating factors of this disease. In these rural districts the people used margarine as their chief fat source prior to the war and marketed their butter, milk and pigs. During the war margarine was no longer available in Denmark; hence the rural populations consumed much more of their own products, including milk, butter and pork.

The possible means by which a high-fat diet might precipitate multiple sclerosis in susceptible persons have been considered elsewhere.[14-18] It is of interest, however, to point out here several respects in which butterfat differs from other fats and oils.[19] First, it is a relatively saturated fat with an iodine value of 45 to 50, compared with olive oil and other vegetable oils, with iodine values of about 90 to 100, and with cod liver oil, with an iodine value of 160 to 175. Secondly, butterfat contains as much as 41 per cent totally saturated triglycerides, a percentage much

higher than occurs in other fats, even when saturated to the same degree. For example, hydrogenation of whale oil from an iodine value of 109 to an iodine value comparable to that of butterfat yields approximately 13 per cent of totally saturated triglycerides.[19] Thirdly,[14] the clustering of the chylomicrons that occurs in heparinized blood in vitro some hours after ingestion of a large butterfat meal is much greater than occurs after a vegetable-oil or codliver-oil meal. Animal fat has the same general characteristics as milk fat, but they are less pronounced. Whether these distinctive characteristics contribute to the possibly greater importance of butter (and probably also animal) fat in the causation of multiple sclerosis has yet to be determined.

The results of the present study and previous observations[5] do not prove that fat determines the relative incidence of multiple sclerosis. However, these observations suggest that this may be so, a suggestion that can only be proved by clinical trial. One of us (R.L.S.) has been employing a low-fat diet containing a maximum of 20 gm. animal fat and 10 to 20 gm. of vegetable oil daily over a period of approximately three and a half years. These studies will be reported in the near future. Because of the unpredictable course of the disease, however, it seems necessary for this hypothesis to be tested by several investigators before its value can be ascertained.

It seems clear from these studies that the incidence of multiple sclerosis in Norway is not significantly influenced by the latitude. This observation, which is contrary to other observations that the incidence does increase in the northern latitudes,[3, 4] may be of significance because of the wide range of latitudes occupied by Norway. The mean temperature is also an unlikely factor, since the coldest parts of Norway are to be found in Opland and Hedmark, where an intermediate incidence rate for multiple sclerosis prevailed, and both a low and high rate of this disease prevailed in much warmer areas, such as those along the entire western coast and on the southern coast of Norway.

It is interesting to note that the mortality rate from circulatory diseases in general in Norway rose prior to the recent war, fell during the occupation period 1941 to 1945 and rose again after the war. These changes likewise ran directly parallel to the average fat intake in Norway during these periods.[20]

Summary and Conclusions

The geographic distribution and incidence of multiple sclerosis has been determined in Norway and correlated with the chief occupation in different areas. These studies suggest that a high incidence of the disease is to be found in farming and dairying areas. The nutrition of inhabitants in both high- and low-incidence areas has been studied. Although not sufficient in number to be of significance statistically, these studies suggest that a high fat intake, — and in particular a high intake of milk and animal fat, — is to be found in the high-incidence areas.

This study seems to corroborate the hypothesis that the ingestion of fats, — in particular milk and animal fats, — may be among the factors that precipitate multiple sclerosis in susceptible persons. Our information does not disprove the possibility that the consumption of these fats may be coincidental with other factors having the same distribution.

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THE DIFFERENTIATION OF PARENCHYMAL LIVER DISEASE AND MECHANICAL BILIARY OBSTRUCTION*

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BALTIMORE

IT IS frequently difficult to differentiate on clinical grounds jaundice due to parenchymal liver disease and that secondary to extrahepatic biliary obstruction. This distinction is obviously essential for proper treatment. In this connection we have found that the determination of the cephalin flocculation, thymol turbidity and serum alkaline phosphatase are most helpful. In an effort to clarify the interpretation of these tests, we have reviewed their employment in the study of 127 jaundiced patients treated at the Johns Hopkins Hospital. In each case the cause of jaundice was clearly established by operation, autopsy or prolonged observation.

CEPHALIN-FLOCCULATION AND THYMOL-TURBIDITY TESTS

Although there are many tests designed to reveal disease of the hepatic cells, the cephalin-flocculation and thymol-turbidity tests are most commonly used at the Johns Hopkins Hospital because they are relatively simple and have a broad reference of comparison in many hospitals. The cephalin-flocculation test and the serum phosphatase in liver disease have been clarified by the important work of Gutman and Hangar.[1] At this hospital cephalin flocculation is measured as 0,+, ++ or +++, and the thymol turbidity is measured in units from 0 to 31 or greater. In 88 consecutive patients without demonstrable liver disease studied at this hospital the cephalin flocculation was 0 or + and the thymol turbidity varied from 0 to 5 units. Values greater than + or 5 units respectively are therefore considered abnormal. In some other laboratories cephalin flocculation is measured as 0 to + to ++++. Two-plus at Johns Hopkins Hospital (and in this series) is equivalent to +++ elsewhere, and +++ in this series is maximally positive. Elevated values are produced by incompletely understood alterations in the serum globulin. Such alterations are usually found in active disease of the hepatic cells, which may be either primary or secondary to extrahepatic biliary obstruction. However, similar changes may also be present in conditions such as disseminated lupus erythematosus, rheumatoid arthritis and infectious mononucleosis, in which hyperglobulinemia occurs in the absence of significant hepatic impairment.[2] In such instances the bromsulfalein test is a more reliable index of liver function than either cephalin flocculation or thymol turbidity.

SERUM ALKALINE PHOSPHATASE

Alkaline phosphatase, produced in bone and liver, is excreted in the bile.[3] The serum concentration of alkaline phosphatase was between 1.5 and 5.4 Bodansky units in 200 consecutive patients studied at this hospital without evidence of disease affecting bone or liver. Elevations above this normal range may result from several factors: Many diseases of bone will cause overproduction of alkaline phosphatase and a rise in the serum level.[4] Among these are Paget's disease, healing fractures, bone metastases, rickets, pressure on bone by adjacent masses and osteomyelitis. It is important to remember that some of these conditions are often asymptomatic. Obstruction of the biliary ducts will elevate the serum alkaline-phosphatase level by interfering with its excretion. This rise will occur when the common bile duct is completely obstructed, but it may also occur when there is only partial obstruction of the biliary outflow. Thus in dogs ligation of one hepatic duct, insufficient to produce jaundice, will cause a marked rise in the serum alkaline phosphatase.[5] When obstruction of the biliary ducts is associated with significant liver-cell damage the elevation of the serum alkaline phosphatase may be less marked than it is in pure obstruction without parenchymal damage, because there is decreased production of alkaline phosphatase by the liver. After total hepatectomy in the dog the serum alkaline phosphatase rises but little, although the dogs rapidly become jaundiced.[3] For reasons that are not entirely clear, elevation of the serum alkaline phosphatase is sometimes observed in patients with diffuse liver disease, such as hepatitis or cirrhosis, perhaps because of blockage of the intrahepatic biliary ducts.[6, 7]

PATTERNS OF LIVER-FUNCTION TESTS IN JAUNDICE

In 79 of the 127 patients studied there was no obstruction of the extrahepatic biliary ducts, and the results of the liver-function tests were as shown in Table 1. The results of the tests in 48 cases with obstruction of the extrahepatic biliary ducts are contained in Table 2.

It is evident that in most of the patients with parenchymal liver disease the cephalin flocculation and thymol turbidity are elevated, whereas the alkaline phosphatase is usually but not always below 15 Bodansky units. In obstructive jaundice,

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the majority of the cephalin-flocculation and thymol-turbidity values are normal, and in most cases the alkaline phosphatase is above 15. It is also apparent that there are cases in which this usual pattern does not apply and in which failure to interpret these laboratory data correctly will sometimes lead to serious blunders. Considered alone, these tests have little value, but when understood in the light of thoughtful observation of the progress of the patients' illness they are of real worth.

Table 1. *Liver Function in Patients With Parenchymal Liver Damage.*

Disease	No. of Patients	No. With Cephalin Flocculation Greater Than +	No. With Thymol Turbidity Greater 5.0 Units per cc.	No. With Alkaline Phosphatase of 5-10 Bodansky Units	No. With Alkaline Phosphatase of 10-15 Bodansky Units	No. With Alkaline Phosphatase Greater than 15 Bodansky Units
Cirrhosis	35	25	28	22	7	6
Hepatitis	34	30	32	17	9	8
Systemic infections other than Weil's disease	10	9	9	9	1	0
Totals	79	64	69	48	17	14

Table 2. *Liver Function in Patients with Mechanical Obstruction.*

Disease	No. of Patients	No. with Cephalin Flocculation Greater Than +	No. with Thymol Turbidity Greater Than 5.0 Units per cc.	No. with Alkaline Phosphatase of 5-10 Bodansky Units	No. with Alkaline Phosphatase of 10-15 Bodansky Units	No. with Alkaline Phosphatase Greater Than 15 Bodansky Units
Carcinoma	25	6	10	1	6	18
Gallstone	20	6	7	2	5	13
Stricture	3	1	1	0	0	3
Totals	48	13	18	3	11	34

Interpretation of Tests

The data contained in these tables and in the literature[8, 9] make it apparent that the cephalin-flocculation and thymol turbidity are often low, even in the presence of marked liver damage (Table 3). We reviewed the course of 14 patients with Weil's disease, proved by guinea-pig inoculation or serial agglutination test. Unfortunately, in only 9 of these were cephalin-flocculation or thymol turbidity tests (or both) performed; all 9 of these are summarized in Table 3. In all 14, however, the serum alkaline phosphatase was determined; this never exceeded 10.4 Bodansky units. Figure 1 shows the relation of the bilirubin and thymol turbidity in 9 cases of Weil's disease and in 9 cases of viral hepatitis selected at random. In Weil's disease the thymol turbidity tends to be much lower than it is in viral hepatitis at any level of hyperbilirubinemia. The reasons for these peculiar circumstances are not clear. They illustrate the point, however, that if the clinical findings suggest parenchymal liver disease and the serum alkaline phosphatase is not impressively elevated, a negative thymol-turbidity flocculation and thymol-turbidity tests are sometimes normal in the presence of parenchymal liver damage. However, this is rare in active viral hepatitis, particularly if the tests are repeated as the illness progresses. In Weil's disease, on the other hand, we have recently noted that the cephalin

Table 3. *Liver Function in Weil's Disease.*

Patient	Range of Serum Bilirubin	No. of Cephalin-Flocculation Determinations		No. of Thymol-Turbidity Determinations		Highest Alkaline Phosphatase
		Normal	Elevated	Normal	Elevated	
	mg./100 cc.					
W. A.	5.8–22.0	1	1	—	—	5.8
J. M.	1.2–18.0	4	0	3	2	7.4
O. S.	12.4–17.5	2	0	—	—	3.7
H. S.	0.8–2.3	2	2	4	0	2.9
C. M.	3.2–23.0	5	3	8	0	4.9
E. S.	4.0–26.4	1	2	2	1	5.8
A. G.	21.6–37.2	6	0	3	3	7.2
H. H.	—–7.3	1	0	—	—	5.5
R. A.	1.2–5.4	4	0	4	0	6.0
Totals		26	8	24	6	

and cephalin-flocculation test do not exclude parenchymal liver disease.

It should never be assumed that elevation of the cephalin flocculation and thymol turbidity of themselves eliminate the possibility that jaundice is primarily due to obstruction of the extrahepatic biliary ducts. These tests will not infrequently become positive if the obstruction has been present long enough to cause hepatic cellular damage. This pattern was observed in 18 of 48 cases in this series.

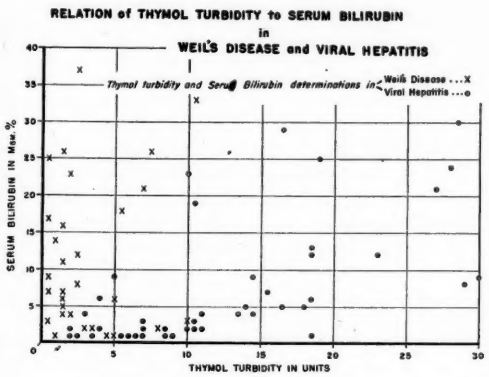

FIGURE 1.

On the other hand, important mistakes will be made if an elevated serum alkaline phosphatase is considered proof *per se* of common-duct obstruction.

We have seen patients with parenchymal liver disease whose serum alkaline phosphatase was as high as 45 Bodansky units. Sometimes the phosphatase rises markedly late in the course of hepatitis or cirrhosis, because of intrahepatic obstruction of the biliary ducts.

CASE 1. D. R. B. (J.H.H. 246137), a twenty-five-year-old Negress, had a history of malaise, low-grade fever, fetor hepaticus and strongly positive cephalin-flocculation test that suggested to some observers that her intense jaundice (bilirubin 23 mg. per 100 cc.) was due to hepatitis. Other physicians thought that the acholic stools, pruritus and alkaline phosphatase of 14.2 units were in favor of mechanical obstruction, and she was therefore explored. The gross and histologic findings indicated acute liver necrosis without evidence of mechanical obstruction. The patient became extremely ill but survived. In the course of the next eight months the jaundice disappeared, but the patient then developed the palpable liver, bromsulfalein retention, collateral circulation and "liver palms" of cirrhosis of the liver. During this period the alkaline phosphatase fluctuated considerably, but on several occasions it was as high as 25 and 31 units.

As previously mentioned, the alkaline phosphatase may be high in the absence of ductal obstruction if there is coexistent disease of bone. This possibility should be kept in mind when an unexpectedly high phosphatase is found.

CASE 2. E. K. (J.H.H. 317418), a forty-three-year-old woman, had undergone a radical mastectomy for carcinoma of the breast. In thirty days her serum alkaline phosphatase rose from 3.9 to 61.3 units, while the bilirubin remained less than 3 mg. per 100 cc. X-ray films revealed metastases in the bones. At autopsy no obstruction of the bile duct was found.

As shown in Table 4 and as reported by others,[10] the serum alkaline phosphatase is not always high in the presence of common-bile-duct obstruction. In only 34 of our 48 patients with obstructive jaundice was it above 15 units. Study of the patients who demonstrated no marked elevation of serum alkaline phosphatase disclosed a variety of reasons for this atypical result. The obstruction of the common duct had been relieved prior to the determination of the phosphatase in some. It is only when persistence of the obstruction is demonstrated by a rising serum bilirubin that one should be surprised to find the alkaline phosphatase low.

CASE 3. V. H. (J.H.H. 251802), a twenty-six-year-old obese Negress, had a history of chronic dyspepsia compatible with jaundice due to gallstones. On admission the serum bilirubin was 7.2 mg. per 100 cc; the alkaline phosphatase was only 5.7 Bodansky units. The serum bilirubin, however, fell to less than 3 mg. within four days and to normal in twelve days. The rapid fall in bilirubin, combined with her history, pointed to passage of a gallstone prior to hospitalization. Subsequently the patient was found at operation to have a patent, normal-appearing common bile duct and a normal liver but a gall bladder full of small stones.

TABLE 4. *Comparison of Liver-Function Tests in Obstructive and Nonobstructive Jaundice.*

CAUSE OF JAUNDICE	NO. OF PATIENTS WITH CEPHALIN-FLOCCULATION OR THYMOL-TURBIDITY DETERMINATIONS (OR BOTH)		NO. WITH ALKALINE PHOSPHATASE BELOW 15 BODANSKY UNITS	NO. WITH ALKALINE PHOSPHATASE ABOVE 15 BODANSKY UNITS
	ELEVATED	NORMAL		
Parenchymal liver disease	69	10	65	14
Mechanical obstruction	18	30	14	34

There may be a lag period before the alkaline phosphatase rises appreciably. This makes serial observations essential to correct interpretation of these tests.

CASE 4. E. M. (J.H.H. 427874), a forty-eight-year-old Negress, was admitted to the hospital with fever, abdominal pain, jaundice, a left-upper-quadrant mass and clay-colored stools. On admission her serum bilirubin was 7.2 mg. per 100 cc. The alkaline phosphatase was only 9.2 units. The cephalin

flocculation was +++ and the thymol turbidity 27. Considered alone, these data might be interpreted as indicative of parenchymal liver disease. Had the patient been operated on at that point, the surgeon would have been gambling unnecessarily. However, the patient was first kept under observation, and in three days the bilirubin rose to 11.2 mg. and the alkaline phosphatase to 23.4 units. At exploration the patient was found to have a dilated common duct, a gallstone impacted at the ampulla of Vater, an inflamed and stone-filled gall bladder and a left subphrenic abscess that contained bile. The site of the apparently sealed biliary rupture could not be found, but the patient recovered uneventfully, after drainage of the abscess, cholecystectomy and emptying of the common duct.

In obstructive jaundice, the degree of elevation of the alkaline phosphatase is influenced by the extent of associated liver damage, as already indicated. For this reason a low phosphatase in the presence of obstruction may be an ominous sign and perhaps a contraindication to immediate operation.

Case 5. A. E. (J.H.H. 409364), a fifty-seven-year-old Negro man, was prostrated with fever and deeply jaundiced. The serum bilirubin was 35 mg. per 100 cc. and the alkaline phosphatase was only 10.9 units. Because his history suggested gallstones, he was operated on. The patient died on the operating table of unexplained vascular collapse — in retrospect probably because of hepatic failure. At autopsy a gallstone was found to be impacted in the ampulla of Vater, but in addition there was marked central atrophy and inflammation of the liver.

In none of the cases we have studied was there proved common-duct obstruction without severe concomitant liver disease in which, if serial determinations were made, the phosphatase remained below 15 units while the serum bilirubin was rising. It thus appears that a serum alkaline phosphatase of 15 Bodansky units is the best approximate dividing line between uncomplicated obstructive and nonobstructive jaundice. It is impossible, however, to be dogmatic about any one figure. No laboratory procedure is that reliable. In one case, for example, the alkaline phosphatase was below 15 units for a protracted period of time, during which the bilirubin remained high.

Case 6. S. T. (J.H.H. 450274), a seventy-three-year-old man, had painless jaundice, minimal digestive symptoms, marked itching and clay-colored stools. During four weeks of observation his bilirubin fluctuated between 23 and 30 mg. per 100 cc., while the phosphatase was 8.8, 9.9, 8.2, 8.7 and 12.2 Bodansky units. Subsequently his phosphatase was 21.2, 24.4 and 24.2 on three occasions. Prior to the finding of high phosphatase levels, exploration revealed an inoperable ductal carcinoma at the bifurcation of the main hepatic duct into right and left branches. Biopsy of the liver showed little evidence of parenchymal damage. Although the phosphatase ultimately became markedly elevated, we are at a loss to explain the relatively low phosphatase over such a long period of time. Fortunately, such cases are decidedly uncommon, but they demonstrate the fallibility of any single laboratory test.

On the other hand, we believe that to ignore the common rules concerning the alkaline phosphatase will much more often lead to the following kind of catastrophe:

Case 7. S. W. (J.H.H. 378231), a fifty-three-year-old colored woman whose past history suggested gall-bladder disease, was admitted to the hospital with jaundice, clay-colored stools and epigastric pain. The serum bilirubin remained around 30 mg. per 100 cc. The cephalin-flocculation test was +++. On three occasions the alkaline phosphatase was 4.7, 6.7 and 4.0 units respectively. Despite persistent indications of parenchymal liver damage and the failure of the alkaline phosphatase to rise on serial determinations in the face of persistent severe jaundice, she was explored under general anesthesia. The gall bladder was found to be full of stones, but the common duct was perfectly normal, and a widespread subacute necrosis of the liver was present. Although the patient had shown slight but definite improvement prior to operation, after surgery she rapidly sank into hepatic coma and died of cholemia ten days later.

Discussion

The serum alkaline phosphatase will frequently point to the correct cause of jaundice if the following qualifications are kept in mind: A high phosphatase unrelated to liver disease may be present when there is coincident disease of the bones. In an important minority of patients with parenchymal liver disease, notably cirrhosis or some forms of hepatitis, the alkaline phosphatase may be very high. In the presence of obstruction of the common bile duct the phosphatase may be relatively low (below 15 units) under the following circumstances: when the obstruction is partial or temporary, as judged by failure of serial bilirubin determinations to show progressive elevation; when co-existent parenchymal liver disease is severe; very early in the course of an obstructive process; and in a rare case for reasons that are not clear. Thus, when there is progressive hyperbilirubinemia due to ductal obstruction and without serious hepatic damage, serial determinations of the alkaline phosphatase will almost invariably reveal levels above 15 units.

The correct interpretation of the alkaline phosphatase is probably the most important laboratory aid in distinguishing parenchymal liver disease and extrahepatic obstruction. Often the cephalin-flocculation and thymol-turbidity tests will give added useful information. Confusion may be encountered when there are concomitant parenchymal and obstructive processes, and in some cases the laboratory data and clinical features point in opposite directions. In either dilemma it is decidedly unwise to base therapeutic management on the laboratory tests alone. Continued observation of the patient's course and serial alterations in these tests will nearly always clarify the diagnosis. In an occasional case the diagnosis will still be obscure. One must then weigh the comparative hazards of continued observation, liver biopsy and exploratory laparotomy.

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FAILURE OF LIGATION OF THE LEFT AURICULAR APPENDAGE IN THE PREVENTION OF RECURRENT EMBOLISM*

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THE problem of systemic arterial embolism in rheumatic heart disease does not end after the patient has survived the acute episode. As protection from re-embolism, which threatens in some 45 per cent of cases,[1] programs based on the use of Dicumarol with ambulatory patients leave much to be desired. Irregular anticoagulant control, further embolism despite adequate control, major hemorrhage and death are recognized complications of this prophylactic method.

Dock in 1946 originally suggested to Madden[2] the possibilities of left-atrial-appendage resection, but the seven reported surgical attempts[1, 3, 4] made since that time to prevent recurrent embolism into the greater circulation have been discouraging. These meager surgical beginnings are reviewed, together with certain newly published[5, 6] and highly significant clinicopathological findings. For comparison the more hopeful, though admittedly relative protection afforded by some recent[7-10] anticoagulant prophylactic programs is presented. Two cases are reported, one successfully managed for nearly two years with ambulatory Dicumarol therapy and one, the fourth reported ligation of an auricular appendage of the embolizing rheumatic heart, with recurrent embolism on the ninth postoperative day.

CASE REPORTS

CASE 1. MRS. A. M. (M. H. 261,751), a 50-year-old woman (a known fibrillator with rheumatic mitral stenosis), was admitted as an emergency 3 hours after experiencing sudden tearing pain in the back and rectum. Aortic saddle embolism was diagnosed. After parenteral administration of papaverine, circulation in the left leg improved considerably. The right leg, however, remained cold and apparently lifeless, without palpable pulsations or oscillations at any level. Five hours after embolism a right-common-iliac embolectomy was performed under novocain anesthesia. The femoral approach was used. Copious quantities of organized clot were suctioned downward from high up in the iliac artery, and the femoral arteriotomy was closed. A single episode of sharp left subcostal pain on the third postoperative day was interpreted as probably resulting from splenic infarction. The patient became ambulatory on the fourth postoperative day. Her responses to Dicumarol being erratic, hospitalization for three weeks was required in an attempt to work out a predictable Dicumarol program for continuous ambulatory use after discharge. Both legs remain warm, and there are bilaterally palpable pulsations at all levels 22 months after embolization. There have been no embolic episodes since Dicumarol therapy was begun and no complications from the therapy despite a major tooth extraction.

CASE 2. MRS. L. R. (W. M. H. 79801/52), a 48-year-old woman, was admitted 14 hours after experiencing sudden severe and prostrating pain in the lower back with radiation down both legs. She had been under treatment for many years with known rheumatic mitral stenosis, aortic regurgitation and auricular fibrillation. On admission the patient was pale, perspiring and apprehensive; she was fibrillating at a rate of 96 beats per minute. Both lower extremities were cold. The right foot and ankle were pale, and the left lower leg was cyanotic, mottled and cadaveric, without pulsations or oscillations below the femoral level. A diagnosis was made of embolism to the left popliteal artery and probably also to the right tibial artery. Because of the long duration and the low levels of these bilateral embolic occlusions, nonoperative treatment was elected. Continuous spinal anesthesia was administered in bed on the ward for 72 hours, together with intermittent intramuscular administration of heparin followed by oral Dicumarol therapy and continuous nasal oxygen. By the 2nd day circulation in both legs had markedly improved, and the patient became ambulatory within a week.

Because of previous lack of co-operation on the part of the patient in ambulatory propylthiouracil management, surgical rather than medical prophylaxis against re-embolism was chosen. Dicumarol was accordingly discontinued, and after her prothrombin level became normal left precordial thoracotomy was performed through the third interspace. A submammary incision was used. The enlarged heart appeared to be rotated almost 70 degrees to the right, partly as a result of the remarkably dilated left auricle. The left appendage shared in the massive dilation of its parent auricle and delivered readily through a pericardiotomy made parallel to and (because of the cardiac rotation) anterior to the phrenic nerve. There was some clear pericardial fluid. A string-like adhesion from the base of the appendage onto the wall of the auricle was utilized much as the belt loops of a pair of trousers, the tape ligature being threaded through this loop adhesion for added security. After its ligation the left appendage was not opened but was thoroughly palpated; no gross mural thrombi could be made out. Postoperative convalescence was smooth, with no chest complications. The patient was able to be ambulatory on the 2nd postoperative day, with no apparent cardiac embarrassment, and there were no significant electrocardiographic changes after surgery.

On the 5th postoperative day the patient complained of sudden, though fleeting, pain with coldness in the sole of the left foot. No definite diagnosis was made, and the foot regained its normal appearance within a few hours. However, on the 9th day after ligation of the left atrial appendage, sudden and sustained pain occurred in the right forearm

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and hand. Associated with this unequivocal episode were pallor, coldness, muscular weakness and absent oscillations and radial and ulnar pulses. Right-brachial-artery occlusion by another embolus was diagnosed, and the right stellate ganglion was blocked with novocain. Heparin and Dicumarol were promptly administered.

The subsequent clinical course has been uneventful. The patient was discharged on the 17th postoperative day. She is now receiving ambulatory Dicumarol therapy, as in Case 1, and has had no further emboli. She has a residual causalgia of the left foot that may require lumbar sympathectomy.

Discussion

Considering the threat of re-embolism in rheumatic mitral stenosis with fibrillation, before ligation or resection of the left auricular appendage can be considered indicated, it must be known to offer probabilities of prevention that are at least comparable to the known results and potentialities of existing medical prophylaxis.

The new surgical approach appears logical provided that there is a reasonable surgical morbidity and mortality; that the appendage can be definitely incriminated preoperatively as the sole source of embolism in a given case; and that no other areas within the circulation are likely to become subsequent sites of threatening mural thrombi.

High postoperative morbidity (3 cases) and mortality (1 case) among the 7 operative cases so far published (Table 1) suggest that surgery should be limited to the simplest effective method, — namely, ligation, — in these poor-risk patients.

Results in terms of re-embolism, however, raise doubts of the wisdom of this type of surgery. Including our own case, 3 of 8 operated cases (Table 1, Cases 1, 7 and 8) have re-embolized within a matter of days. Analysis of recent autopsy series reported by Daley and his co-workers[5] and by Jordan's group[6] suggest that at least this number of surgical failures might in retrospect have been predicted.

In Daley's series,[5] autopsies were performed on 39 of 194 cases of rheumatic heart disease in which embolism had occurred in the systemic arterial circulation. Jordan[6] analyzed 51 cases of rheumatic mitral stenosis with intracardiac mural thrombi from among 11,536 autopsies. Only 10 of Daley's cases, or approximately 26 per cent, showed thrombi limited solely to the appendage of the left atrium. After a strict breakdown of Jordan's 51 cases, 10 mural thrombi, or approximately 20 per cent, emerge as exclusively intra-appendage clots. Thus an average of 23 per cent of thrombi, in 90 post-mortem examinations of embolizing or potentially embolizing rheumatic hearts, were strictly limited to the left atrial appendage.

From these data it follows that over three quarters of patients operated on undergo useless exclusions of appendages that either are empty or are not the sole source of future emboli. Half the predicted 75 per cent of surgical failures are already apparent (3 of 8 cases, Table 1). Through the mere passage of time, at least 3 more of these 8 cases are likely to re-embolize. Indeed, since the operations can not deter them, new thrombi may form post-operatively to threaten from additional diseased sites within the heart, and one may conceive of an eventual 100 per cent failure of the surgical method.

What, on the other hand, are the results and potentialities of ambulatory anticoagulant therapy? At the outset, it must be admitted that such management provides a degree of over-all protection from embolism, be the source any portion of either the left or the right heart cavities.

Long-term anticoagulation therapy in general is relatively new; it is being studied by a number of groups.[7-11] Sprague and Jacobson[9] were among the first to apply successfully the new method specifically to the prevention of recurrent embolism in rheumatic heart disease; their original patient has now lived for three years without emboli or complications. Cosgriff has the largest series; he has treated 17 patients with embolizing rheumatic heart disease on a program of continuous Dicumarol therapy for a total of 200 months. This is equivalent to about sixteen years of treatment without embolism or mishap. The vehicle, it is true, is still too new for definitive evaluation. However, if recent surgical measures seem rather hopeless, these preliminary experiences with anticoagulant prophylaxis are most encouraging. In the light of present knowledge, as briefly outlined, and until intracardiac thrombi can be satisfactorily localized, preventive

Table 1. *Surgically Treated Left-Auricular Appendages in the Prevention of Systemic Arterial Re-Embolism.*

Case	Author	Operation	Morbidity	Follow-up Interval	Result
1	Madden[2] (1949)	Appendectomy	Cardiac arrest	8 months	Left hemiplegia at operation
2	*Idem.* (1949)	Appendectomy	None	9th day	Died (no autopsy)
3	Baronofsky and Skinner[3] (1950)	Ligation	None	4 months	Well; no re-embolism.
4	*Idem.*	Ligation	None	3 months	Well; no re-embolism.
5	*Idem.*	Ligation	None	2 months	Died
6	Beal, Longmire and Leake[4] (1950	Appendectomy	Thoracentesis	8 months	Well; no re-embolism.
7	*Idem.*	Appendectomy	Thoracentesis	1 month	Numb cool right foot with diminished popliteal pulse on 7th day
8	Leonard and Cogan (1952)	Ligation	None	5th day 9th day	Fleetingly cold painful left foot Sustained cold pulseless right forearm

*An additional case, a right appendectomy, is omitted from this study of systemic arterial re-embolism control.

appendage surgery should, we believe, be abandoned in favor of modern anticoagulant methods.

Summary

No preoperative diagnostic method is so far available to locate parent mural thrombi in embolizing rheumatic heart disease. Only 23 per cent of these embolic sources were found at autopsy to be limited solely to the left atrial appendage. Anticoagulation therapy, as briefly outlined, offers a more rational and effective prophylactic approach at the present time. We believe that ligation or resection of the left atrial appendage should be abandoned until diagnostic methods are developed to delimit intracardiac thrombi preoperatively. Two cases of rheumatic mitral stenosis with fibrillation and systemic embolism have been reported; 1 patient continues well without re-embolism after twenty-two months of continuous Dicumarol. The second patient, who underwent the fourth reported ligation of an auricular appendage of the embolizing rheumatic heart, required anticoagulant therapy because of recurrent embolism on the ninth postoperative day and is doing well at the time of this report.

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TRIPELENNAMINE DYSURIA IN CHRONIC NEPHRITIC UREMIA*

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ACCORDING to recent estimates as many as 10,000,000 people will be taking antihistamines in the United States this year,[1] and 6 to 16 per cent of them will experience side-reactions.[2] Among the less well known reactions accompanying the use of these agents is difficulty in initiating and maintaining the urinary stream, with associated symptoms of urinary obstruction. In 1949 Wolfson[3] reported the occurrence of urinary obstruction in a patient who received tripelennamine. Although reference has been made to this untoward effect[1, 2, 4-8] in the literature, no other case reports for this agent were found. Physicians' awareness of this disturbing symptom may forestall needless and possibly dangerous local manipulation. Because the uremia from which our patient was suffering may have played an accessory role in this particular form of sensitivity, and since investigative endoscopy was contraindicated, the following case record seemed worthy of attention.

Case Report

J. P., a 36-year-old man, was admitted to the Beth Israel Hospital for the first time on September 12, 1951, because of difficulty in urinating for 2 weeks. His past medical history disclosed an attack of pneumonia and poliomyelitis during childhood; he had had two surgical operations, one for correction of a foot deformity (left) due to poliomyelitis and the second for acute appendicitis. During his early adult life he began to suffer from seasonal allergy (during August and September) that had been relieved by progressively smaller doses of pyribenzamine within the past 4 years, requiring 200 to 250 mg. daily in 1947 and only 12½ to 50 mg. daily in 1951.

Nine years before admission proteinuria was discovered during an examination for life insurance, and for the past 6 years hypertension had been present. Nocturnal dyspnea appeared 1½ years ago. Progressive heart failure during the past 2 months necessitated the introduction of digitalis and mercurial diuretics. Because of urinary frequency and difficulty in initiating the urinary stream, he consulted a urologist during September, 1951, who found uremia without commensurate local disease and referred him for further study.

Physical examination revealed a pale man who had periorbital puffiness. In addition to increased tortuosity of the fundi, there was a whitish exudate in the left retina. Triple heart rhythm was audible in the left third interspace. The prostate was small, smooth and nontender. There was no peripheral edema. Atrophy of the left calf muscle and a flexion deformity of the first toe were the sole remnants of the attack of poliomyelitis during childhood.

Urinalyses revealed a specific gravity of 1.010 to 1.014, with 0 to ++ protein. There were 1 to 3 red cells and from a few to many white cells per high-power field. Examination of the blood revealed a normochromic anemia with 13 per cent eosinophils. The erythrocyte sedimentation rate was 106 mm. per hour (Westergren).

The blood glucose was 113 mg., the urea nitrogen 100 mg., the nonprotein nitrogen 130 to 140 mg. and the creatinine 8.4 mg. per 100 cc.; the serum sodium was 130.1, the serum potassium 4.2 and the serum chlorides 100 milliequivalents per liter. A blood Wassermann test was negative.

Roentgen study of the chest revealed that the heart was enlarged, particularly in the region of the left ventricle. The aorta was wide and elongated. Intravenous pyelography showed very faint visualization of the right kidney; the left was not seen. An electrocardiogram revealed a normal sinus rhythm and left-axis deviation. The RST complex was depressed in Leads 1 and 2. The initial urine specimens contained staphylococci, but none were found after the introduction of penicillin therapy. The venous pressure was 35 mm. of water. The Decholin arm-to-tongue time was 15 seconds; the ether arm-to-lung time was 7 seconds.

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Because of the occurrence of dysuria 2 weeks after continuous pyribenzamine ingestion, the drug was withheld. The patient was maintained on digitoxin 0.1 mg. daily and phenobarbital 0.015 mg. four times daily. After the adoption of this regimen, he improved progressively; the dysuria subsided in 5 days and he was easily able to start micturition. When he was completely relieved of these symptoms, tripelennamine was again given, this time in elixir form, in doses of 30 mg. 4 times daily. On September 22, 1 day later, difficulty in urination reappeared, and after 2 days severe dysuria was present. The total dose for this period was 270 mg. The drug was again stopped and all symptoms were relieved within 3 days. Penicillin was then administered in order to correct the bacteriuria and pyuria; the uremic status, however, remained unchanged. In order to establish beyond all doubt that tripelennamine was the source of this patient's symptoms, a blind test was performed. Similar yellow capsules were prepared; half of these contained only lactose. From October 5 to October 10, one lactose capsule was given 3 times daily, and except for a minimum amount of burning on urination on a single occasion, mentioned only after questioning, there were no complaints. On October 11, without the knowledge of either the patient or his attendants, the pyribenzamine capsules were given; after the third capsule, the patient again had difficulty in micturating. This increased in intensity so that after the sixth capsule was taken (300 mg.) he could no longer start or maintain the flow of urine. After the drug was withdrawn the patient became asymptomatic in 2 days. His urinary output during his entire hospital stay was always well above 1 liter daily.

The patient was discharged with a diagnosis of chronic nephritis, uremia and hypertension.

Discussion

Although individual reports mentioning urinary disturbances following ingestion of antihistamines are found in the literature, we were able to discover only 2 well documented cases, one caused by tripelennamine[3] and the other by phenindamine.[6] *New and Nonofficial Remedies for 1951*[9] and *Grollman's Textbook of Pharmacology* (1951)[10] do not list the genitourinary side-effects of these drugs. Although the more serious untoward reactions, such as convulsions,[9] agranulocytosis[2, 11-13] and hemolytic anemia,[2] have been emphasized, dysuria, with the exception of frequency, has been given scant attention.[7] We have regarded this untoward reaction in a uremic patient principally as a side response to tripelennamine. The impaired kidney function probably played a distinct if minor role in prolonging the symptoms as a result of inadequate renal excretion. Perlman has reported that about 10 per cent of tripelennamine is excreted in the urine in a conjugate form,[14] the primary metabolic disposal of this substance occurring in the liver.[15] Because the small size of the pyribenzamine molecule makes it readily filtrable at the glomerulus, only a patient with severe renal impairment would present evidence of cumulation with the small doses taken in this case. Then, too, the decreasing need for tripelennamine over a four-year period may have reflected the diminishing renal reserve resulting from chronic glomerulonephritis. The dose required to initiate the abnormal urinary symptoms was regarded as evidence of unusual sensitivity. However, the persistence of symptoms for seven days after drug withdrawal may be interpreted as a sign of cumulation.

Inability to urinate without concomitant disease recalls a reaction frequently observed in patients with atropine poisoning,[10] who although wishing to void cannot do so. Atropine, as an anticholinergic substance, blocks the postganglionic cholinergic fibers of the parasympathetic chain. Tripelennamine possesses a mild atropine-like action and is therefore similarly anticholinergic.[16] It is suggested that other antihistamines having anticholinergic effects because of their slight atropine-like action will produce identical effects. The specific effect on micturition is related to the reciprocal action between the contracting bladder wall and the relaxing vesical detrusor under the influence of cholinergic stimulation, the opposite effects occurring, as they did in this case, with an anticholinergic drug such as tripelennamine.

The temptation to use the methane of β methylcholine in a patient with such symptoms is easily resisted when one recalls the dangerous bronchoconstrictor effects occurring in asthmatic patients when cholinergic drugs are administered.

This clinical physiologic experiment might answer the question whether the epinephrine-like rather than the atropine-like effects are responsible for the occurrence of the vesical spasm and urinary obstruction in a patient exhibiting these symptoms.

Of other unusual genitourinary effects observed after the use of tripelennamine, reduction in potency has been mentioned by Baer, Sulzberger and Witten[8] and has also been observed by one of us in a patient who recovered promptly after the withdrawal of tripelennamine.

Summary and Conclusions

A patient with chronic nephritis and uremia observed increasing difficulty in voiding after he took small doses of tripelennamine. Withdrawal of the drug resulted in complete relief of this symptom in seven days. Subsequent controlled ingestion of the drug on two separate occasions was promptly followed by identical symptoms, which again were relieved by withdrawal.

The mild atropine-like anticholinergic effect of tripelennamine on the detrusor of the bladder apparently produces vesical-sphincter spasm and paresis of the bladder wall.

Uremia probably played an auxiliary role in producing rapid cumulative action of this antihistamine because of impaired renal excretion. The presence of azotemia should indicate cautious administration of tripelennamine.

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MEDICAL PROGRESS

THE CASE FOR WATER FLUORIDATION*

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FLUORIDATION of community water supplies is one of the truly important developments in the field of preventive dentistry. Current discussion of this measure brings to mind another preventive health technic, — inoculation against smallpox, introduced in the American colonies 231 years ago.[1]

Inoculation made quite a stir. It was a success from the beginning, but it created so much excitement and opposition that those who submitted to it were considered a public menace. One of its ardent supporters, Cotton Mather, turned his home into a secret inoculation center. Even as late as 1774, a hospital here in Salem was burned for fear that it would be turned into a hospital for inoculation. Yet today, due to inoculation and later to vaccination, smallpox is virtually unknown in this country.

This is an example of how every great public-health measure has met with a certain degree of organized opposition before it was finally accepted. This has been true of pasteurization of milk, chlorination of water and all the rest. Controlled water fluoridation, hailed as the most important development in the history of preventive dentistry, is no exception.

It is now more than a year since the American Dental Association put its stamp of approval on water fluoridation as a mass method of reducing the incidence of tooth decay by 65 per cent. Similar endorsements have come from all the other national groups concerned with promoting dental health — the American Public Health Association, the American Association of Public Health Dentists, the American Medical Association, the U. S. Public Health Service and many others.

These highly reputable organizations did not give their blessing lightly. They approved fluoridation only after careful study by competent members and consultants, experts with broad scientific knowledge in every phase of fluoride chemistry and toxicology.

Yet progress has been far too slow. There are well over 16,000 public water supplies in this country, but at present less than 1 per cent of them have been adjusted to bring to the consumer this truly remarkable public-health measure.

The situation is much the same here in Massachusetts. The fluoridation program has been endorsed by your own State Department of Public Health and by your state dental society. The Massachusetts 4-H Clubs, the Parent-Teachers Association and any number of local groups are for it, too. The Massachusetts Medical Society approved fluoridation in May, 1951.

Yet, with a population exceeding 4,500,000, less than 30,000 persons in Massachusetts are now drinking fluoridated water. Of the 263 communities with public water supplies in this state, only 4 have actually given their children the privilege of drinking fluoridated water. I use the word "privilege" in its true sense. It is the privilege of having straighter, stronger, better-looking teeth than their parents have had, of having two thirds fewer cavities and extractions than their parents have had.

It is rather surprising to note that no more than 4 communities in Massachusetts have fluoridated their drinking-water supplies, when we realize that each of us can buy this privilege for about 10 cents a year, and particularly when we realize that every dollar spent for fluoridation will erase the need for spending 60 or 70 times that amount on fillings, extractions and replacements.

*Presented at the regional meeting of the North Shore District Dental Society, Salem, Massachusetts, January 17, 1952.

†Chief, Division of Dental Public Health, U. S. Public Health Service.

The reluctance to accept fluoridation on a statewide scale is still more surprising when we recall a passage in the fluoridation policy statement of the Massachusetts Division of Dental Health: "It has long been established that Massachusetts citizens suffer from dental decay to an alarming degree. . . . It is the rare Massachusetts resident who does not need a dentist's attention at least yearly because of the damage produced by tooth decay."[2]

Why, then, is the fluoridation program moving ahead with all the speed of the proverbial snail, in Massachusetts and elsewhere in the country? Why are we quibbling, delaying, pigeon-holing — in the face of exhaustive research and overwhelming proof?

Public indifference, sheer inertia, may be one reason. When people turn out for meetings such as this one, however, and when I see their interest and enthusiasm, I am not at all sure that public indifference is the main reason.

Another, and probably more valid, answer is that the vast majority of us are conservative, slow to accept change. As I mentioned at the beginning of this talk, every public-health measure, every major change, has met with determined and often heated opposition before finally being accepted on a broad scale.

And now I come to what I believe to be the chief reason for our slow progress: lack of information, misinformation, or both. Unless we public-health workers, dentists and parents take immediate steps to correct this misinformation, at the rate we are going the fluoridation job will not be done for at least 150 years. It is a job that actually can and should be accomplished in not more than from three to five years.

I do not believe, however, that you are going to let it take that long once you, your colleagues and your neighbors know the facts. These facts prove that it is too costly, both in dollars and health, for any community to delay fluoridation a single day.

What are the facts? In the simplest terms, they are these:

That an infinitesimal quantity of fluoride compound added to a community water supply will reduce tooth decay by as much as two thirds.

That this protection against dental decay will carry over to the future generations of adults.

That it will save many millions of dollars in dental bills for those of us who are now receiving adequate dental care. I should like to point out, however, that since tooth decay in this country is occurring six times faster than our dentists can repair it, American children are getting only a fraction of the fillings they require. Thus, instead of reducing the nation's over-all dental bill, fluoridation will bring us much nearer to the goal of adequate dental care for all our people.

All these things can be accomplished by adding fluoride to community water supplies in scientifically controlled amounts. It is a process that does not change the odor, taste or color of water. It can be done simply and so inexpensively that for a total cost of about the price of one filling the average American can drink fluoridated water for his entire life.

Perhaps the most important single fact about fluoridation is that it will not harm any living thing or interfere with any industrial process. Except for its remarkable benefit to teeth, fluoridation will not affect us, our surroundings or our way of life in any manner whatever.

This, then, is the case for fluoridation. The facts of the case can be told simply and briefly. Behind these facts, however, lies a mass of proof based on years of painstaking scientific research — because fluoridation is no magic formula concocted overnight.

The theory that tooth decay might be related to fluorine deficiency in the diet was first suggested in England as far back as 1892.[3] Sixteen years later, Dr. Frederick S. McKay, of Colorado Springs, decided to find out why some children in his state had mottling of the teeth. He discovered that something in their drinking water caused the mottling, known as "Colorado brown stain." McKay also noted that mottled teeth were more resistant to decay.[4]

However, not until 1931 did scientists prove that excessive amounts of fluorine in drinking water were causing both the mottling and the resistance to decay.[5, 6] This observation led to detailed studies of the relation between dental decay and fluorine in water supplies. Studies of this kind were conducted not only in this country[7, 8] but also in England,[9-11] Sweden,[12] Switzerland,[13, 14] Italy,[15] India[16, 17] and Africa.[18] The results of these investigations were amazingly uniform.

They indicated clearly that tooth-decay rates decrease as the fluoride concentration in drinking water supplies increases from none to about 1.5 ppm. They also proved conclusively that children born and reared in communities having from 1.0 to 1.5 ppm. of fluoride in drinking water have two thirds less tooth decay than youngsters in non-fluoride areas, such as Massachusetts (Fig. 1).

Last year a dental survey was made in 28 typical Massachusetts communities where the drinking water contains practically no fluoride.[19] Several years ago a similar survey was conducted in 6 Illinois cities that have fluoride concentrations ranging from 1.2 to 1.8 ppm.[20] A comparison of the two gives a dramatic illustration of the benefits of fluoridated water. Comparing only the rates in the age groups from twelve through fourteen, we find that Massachusetts children had four times as many decayed, missing or filled teeth per child as youngsters in the 6 Illinois communities.

All these investigations not only have proved that children have fewer cavities when they drink water containing from 1.0 to 1.5 ppm. of fluoride — they also show that these same children do not suffer from mottled enamel.

If this small amount of natural fluoride reduces tooth decay without mottling teeth, the researchers

NUMBER OF CITIES STUDIED	NUMBER OF CHILDREN EXAMINED	NUMBER OF PERMANENT TEETH SHOWING DENTAL CARIES EXPERIENCE* PER 100 CHILDREN EXAMINED (0 100 200 300 400 500 600 700)	FLUORIDE (F) CONCENTRATION OF PUBLIC WATER SUPPLY IN P.P.M.
11	3867		< 0.5
3	1140		0.5 TO 0.9
4	1403		1.0 TO 1.4
3	847		> 1.4

FIGURE 1. *Dental Caries (Permanent Teeth) Observed in School Children 12 to 14 Years of Age in 4 States, According to the Fluoride Concentration of the Public Water Supply. (Reproduced from Dean.*[8])

*Dental-caries experience is computed by totaling the number of filled teeth, the number of untreated carious teeth, the number of teeth requiring extraction and the number of teeth missing (presumably because of caries).

reasoned, why could not the same effect be gained through scientific control?[21] The theory that a two-thirds reduction in dental decay might result from bringing the fluoride content of water up to the level of 1.0 ppm. led to a series of controlled

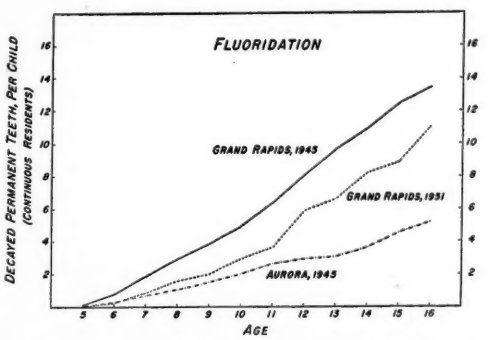

FIGURE 2. *Dental Decay (Permanent Teeth) in Children of Grand Rapids and Aurora.*

fluoridation studies, beginning in 1945 in Grand Rapids, Michigan,[22, 23] Newburgh, New York,[24] and Brantford, Ontario.[25] During the years that followed, similar projects were undertaken in other communities.[26-29]

The purpose of these studies was not to determine whether or not 1.0 ppm. of fluoride in water is a safe amount. We already knew that, simply because millions of Americans have been drinking water containing this amount of natural fluoride all their lives without ill effect.[30] The purpose was to determine whether or not controlled fluoridation would produce the same results as natural fluoridation, in the amount of from 1.0 to 1.5 ppm. Many of these studies have been under way for six or seven years, and in each case the answer has been an unqualified "yes."

Consider the case of Grand Rapids, an industrial metropolis about equal in size to the city of Worcester. Like Worcester, Grand Rapids had no natural fluoride in its water supply. Figure 2 gives a clear illustration of the dental-decay situation in that city in 1945. The top line shows the amount of decay in permanent teeth of school children, grouped according to age. It represents the average number of carious teeth per child. Notice that the average sixteen-year-old in Grand Rapids had about 14 carious teeth.

The bottom line represents the tooth-decay rates among children in Aurora, Illinois, where drinking water contains 1.2 ppm. of natural fluoride.

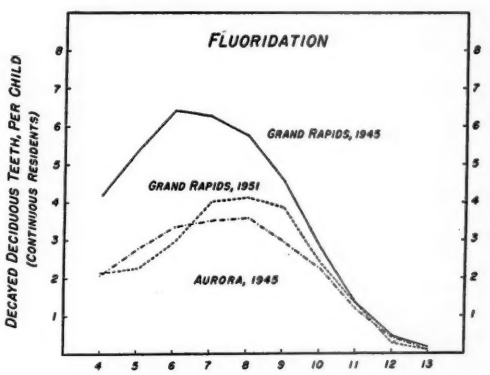

FIGURE 3. *Dental Decay (Deciduous Teeth) in Children of Grand Rapids and Aurora.*

You can see that sixteen-year-olds in Aurora had only 5 decayed permanent teeth, approximately one third as many as the same age group had in Grand Rapids.

The center line shows what had happened in Grand Rapids by 1951, six years after the start of fluoridation.[22] To understand this line, you must realize that we had known all along that only children born and reared on fluoride water would receive its fullest benefits. All we had a right to expect, therefore, was that six years after fluoridation began children six years old or younger in Grand Rapids would have the same decay rates as their opposite numbers in Aurora. After all, the seven-year-olds were one year old at the beginning of

fluoridation; eight-year-olds were two, and so on. Surprisingly enough, the older children benefited also. In the age groups from seven through eleven decay rates in Grand Rapids are already more than halfway down to the Aurora level.

For seven years now, Grand Rapids has been putting fluoride into its water supply at a cost of less than 10 cents per person a year.[31] In return for this tiny sum, the city has gained far better teeth for its children. Five-year-olds, born before fluoridation, have about 74 per cent fewer caries than children in the same age group had seven years ago. The decay rate has dropped 66 per cent in children one year older, who were born at about the same reached middle age the natives of Boulder had lost three to four times as many teeth from decay as had persons of the same age in Colorado Springs.

So much for the facts about fluoridation, the information you need to have when your community is considering fluoridation. I should like now to touch upon a matter I mentioned earlier — the subject of misinformation. The rumors and half truths to which I am referring are often circulated by sincere persons who are misled either by emotional prejudice or by lack of knowledge. These opponents of fluoridation have made many charges against the program, but not one of their objections is supported by fact.

TABLE 1. *Post-Fluoridation Reductions in Dental Caries.*

PLACE	DATE FLUORIDATION STARTED	REPORT PERIOD	AGE GROUP	PERCENTAGE OF CARIES REDUCTION
Evanston, Illinois	February, 1947	After 12-13 months	6	49.8 DMF†
			7	32.5 DMF
			8	22.3 DMF
Marshall, Texas	May, 1946	After 29 months	6	47.0 DMF
			All school ages	23.0 DMF
Newburgh, New York	May, 1945	After 4 years	6–12	33.0 DMF
Lewiston, Idaho	June, 1947	After 3 years	7	58.0 DMF
			8	35.0 DMF
Sheboygan, Wisconsin	March, 1946	After 4½ years	Kindergarten	46.0 DEF*
			4th grade	31.0 DMF
Brantford, Ontario	June, 1945	After 54 months	6	56.0 DMF
			8	43.0 DMF
			12	22.0 DMF
			14	20.0 DMF
Grand Rapids, Michigan	January, 1945	After 5 years	6	Caries experience is conforming to curve — found in places with natural fluoride 1 to 1.5 ppm.— as Aurora, Illinois, where the fluoride is 1.2 ppm.
			7	
			8	

time fluoridation was started. The decline is about 45 per cent for seven-year-olds, 40 per cent for eight-year-olds and so on, with the benefits lessening slightly for each additional year. Even in the sixteen-year age group there has been a drop of nearly 16 per cent, and the crowns of the permanent teeth of these youngsters had fully formed before fluoridation was introduced in Grand Rapids. Figure 3 shows an identical trend in the caries experience in the deciduous or baby teeth of these children.

Results have been similar in every city that has been fluoridating its water on a study basis (Table 1). We are not guessing, therefore, when we predict what would happen should Worcester or any other Massachusetts community start fluoridating tomorrow: Infants born in 1952 or later would have 65 per cent fewer caries by the time they are six than they will have without fluoridation.

These benefits are not temporary; they last a lifetime. This was demonstrated last year by a study of the teeth of adult residents of Boulder, Colorado, a fluoride-free community, and Colorado Springs, which has had 2.5 ppm. of natural fluoride in its water for at least sixty years.[32] Russell, of the Public Health Service, found that by the time they

Some of the charges are so flimsy and fantastic that were we to take them seriously we would have to admit that we have progressed no further in our thinking than the days of witchburning and black-magic superstition. Some of these objections are serious, however, because they are based on only part of the truth and are being set forth in such dramatic terms that they threaten to hold up the entire fluoridation program.

This is why I should like to discuss some of the more serious charges, discussing them one by one and demonstrating that they are neither factually sound nor even logical. Some of them, in fact, are downright falsehoods.

First, there is the common argument that fluoridation is a form of "mass medication."

Fluoridating water to prevent tooth decay is no more a mass medication method than is chlorinating water to prevent typhoid or iodizing salt to prevent goiter or enriching milk and bread with Vitamin D to prevent rickets. Mass medication means mass *treatment*, and no one has ever claimed that fluoridation will treat or cure existing cavities in the teeth.

A pamphlet written by one fluoridation opponent likens a child to "a lily the edges of which are turn-

ing brown." According to this writer, "you are asked to correct the situation by painting the lily white."

Unfortunately, the man is misinformed. He misses the point entirely.

In the same vernacular, I can reply that fluoridation does not gild the lily by treating cavities, but it does prevent much of the need for gilding the lily by preventing two thirds of the cavities from ever getting started.

Some fluoridation opponents are worried about what they call "tampering with nature."

To them I should like to point out that fluoride is not a foreign agent in water. It is a normal constituent of many water supplies throughout this and other countries, ranging in amount from a mere trace through the ideal range of 1.0 to 1.5 ppm. and so on up to definitely excessive concentrations.[30]

In the same vein, there is another common argument that fluoridation is undemocratic and destroys our civic rights guaranteed by the Constitution. This is not true, of course. We have been chlorinating our water supplies for nearly fifty years without losing any of our civic rights. It must be remembered, too, that fluoridation has not been and cannot be adopted by any community without first passing through all the traditional democratic processes. It must be approved by the state dental society and the local health department, and it must have substantial public support. It must be endorsed and formally approved by the city fathers. The health department must supervise the project, making certain that it is subject to all the necessary scientific controls. All this must be done at the local community level. It would be impossible for any state or Federal official or government to order a community to fluoridate its water. Fluoridation cannot, in other words, be foisted on any community.

Perhaps the most common, and surely the most alarming, of the charges leveled against fluoridation is the claim that it is dangerous, and that those who advocate it are trying to "poison our water supplies." This is a perfect example of what I meant by "misinformation," because these arguments are based solely on half-truths about the physiologic effects of fluorides.

It would be unwise to brush these objections aside — they should be analyzed critically and dispassionately, so that there will be no doubt in anyone's mind that controlled fluoridation is a completely harmless public-health measure.

In the first place, we all know that sodium fluoride and the other fluoride compounds are toxic. Perhaps some of us do not realize, however, that fluoride is poisonous only when consumed in excessive amounts. I cannot overemphasize the phrase "excessive amounts," since it seems to be the unspoken basis for most of the arguments against fluoridation.

We know that fluoride is toxic in excessive amounts. So is baking soda, for that matter, and so is chlorine. In fact, nearly everything we eat and drink is harmful when consumed in excess. Vitamin D, for example, has practically wiped out the dread disease of rickets in this country, but it is also known to be toxic in massive doses. As for fluoride, you would have to drink over 400 gallons of water containing 1.0 ppm. at one sitting to receive a toxic dose.[33] Such a large drink of water might kill you, of course, but water alone would do the job without any help from fluoride.

How can we believe that fluoridation poisons public water supplies when we realize that more than 3,000,000 Americans have lived all their lives in naturally fluoridated areas?[30] In regions where water contains from 1.0 to 1.5 ppm. of natural fluoride, the natives are at least as healthy as you or I, and they have far better teeth. This is a fact that cannot be successfully disputed by even the ardent opponent of fluoridation—not if the argument is based on fact.

There have been rumors (and these are not even half-truths) that the recommended fluoride concentration can cause, or contribute to the cause of, any number of dire ailments, ranging from cancer and nephritis to discolored teeth. Not one speculation of this kind has ever been substantiated.

I shall discuss briefly one of the many research studies that contradict these alarming claims. The Wisconsin State Board of Health singled out 3 cities with varying degrees of water fluoride content, comparing their mortality rates from the nine leading causes of death: heart disease, cancer and so forth.[34]

The cities surveyed were Green Bay, which for forty years has had twice as much fluoride in its water as the scientifically recommended amount; Fond du Lac, with a fluoride content of only 0.45 ppm. in its water supply; and Sheboygan, where drinking water contains scarcely any fluoride. The survey covered the five-year period from 1940 to 1945; it showed clearly that there was no relation whatever between death rates and the quantity of fluoride in water.

Some of the rumors linking fluoridation to disease have stemmed from the fact that fluoride can cause certain ailments — but again, this is true only when it appears in water in excessive amounts. A series of investigations has demonstrated that when fluoride is present in concentrations of 12.0 ppm. or more there may be signs of undesirable changes in bone structure.[35-40]

Such situations, however, are invariably alike in one respect. When they do occur, it is always in communities where drinking water contains at least 12 or 15 times the quantity recommended for controlled fluoridation.

There are those who will say that people who drink fluoridated water over a long period of years may become afflicted with fragility of the bones, resulting in frequent fractures and other bone ail-

ments. This is certainly not true in areas where water fluoride content is at the optimum of 1.0 to 1.5 ppm., or even five times that amount. In fact, the results of fluorine-balance studies show that a remarkably efficient excretion of fluorine is a normal kidney function in adults.[16, 33, 41-44]

A study of approximately 4000 high-school boys and Army selectees from different parts of the country indicated that there is no relation between bone fracture and continuous exposure to fluoride water containing 2.0 ppm. — or even 4.0 or 5.0 ppm.[43] The competent physicians who carefully examined these 4000 young men could not find a single case of bone fragility caused by fluoride, even when fluoride content was many times the optimum of 1.0 to 1.5 ppm. It is also worth noting that none of the boys differed in height or weight from the accepted standards of this country.

I should like to point out, also, that in some parts of the United States there are water supplies with natural fluoride concentrations as high as 8 and 10 times the quantity prescribed for controlled fluoridation; the fluoride concentration in one town in Texas is 18.0 ppm.[45] Yet not one actual proved case of chronic fluoride poisoning, with the exception of mottled enamel, has ever been reported in this country.[46] Remember this whenever you hear a rumor about some disease or other physical defect supposedly caused by drinking fluoridated water. It might be wise, the next time you hear such a rumor, to ask this one simple question:

"How much fluoride did the drinking water contain?"

It is highly improbable that your informant will know the answer, but if he does, he will have to admit that the water in question contained many times the amount recommended for controlled fluoridation.

I spoke a moment ago about mottled enamel, and I should like to quiet any fears you may have on that score. It has been suggested that if we fluoridate community water supplies our children may develop mottling. This is a natural fear, perhaps, since it was mottling that led to the original discovery that fluoride reduces tooth decay. It is an unnecessary fear, nevertheless, since it takes an excessive amount of fluoride to cause mottled enamel.

In any community, fluoride or non-fluoride, some children drink more water than others. An athlete probably consumes more water than a bookworm. This variation in individual water consumption, however, is no more peculiar to communities with controlled water fluoridation than to those with optimum natural fluoride in their water. You will recall that it was the extensive studies of the teeth of children in communities with natural fluoride that established the optimum fluoride concentration.[8]

On the subject of mottling, the American Medical Association stated recently:

> From the available evidence based on thousands of observations, the incidence of mottling of the enamel of children who drink water containing fluoride up to a concentration of 1.0 ppm. is minimal. . . . It occurs only in a small percentage of children and is so slight as not to present a problem from the point of view of appearance or strength of the teeth.[47]

The opponents of fluoridation will be hard pressed to quarrel with this statement from a group representing the organized physicians of our country.

It will also be difficult for them to challenge the National Research Council, another venerable scientific body, which said recently:

> The margin between the optimal quantity of fluoride in drinking water which is required for maximal benefit in tooth development, and the amount which produces undesirable physiological effects is sufficiently wide to cause no concern.[48]

This simple statement is a good summation of the case for fluoridation. It contains none of the drama or emotional appeal of some of the pamphlets being circulated by the opponents of fluoridation. The pamphlets are based on fear and misunderstanding. The National Research Council's statement, on the other hand, is sober and unemotional. It is founded on a thorough scrutiny of the facts, a detailed examination of all the evidence by an organization dedicated to the study of every scientific project affecting the national welfare.

I am sure that you, too, will agree that the evidence in favor of fluoridation is pretty conclusive. A careful study of the pros and cons discloses not one particle of evidence to support any objection ever raised against the measure. The objections simply do not stand up, once thinking persons know the facts.

We are all familiar with the constant struggle to convert atomic energy to constructive, instead of destructive, uses — to use it for healing and not killing. Science has already been able to accomplish much the same feat in regard to sodium fluoride and the other fluorine compounds. After years of research and testing, science has succeeded in converting fluoride into a health benefit for the nearly 100,000,000 Americans who are now served by public water supplies.

Ninety-eight per cent of our people are afflicted with dental decay, the most widespread of all diseases. Scarcely an American family escapes it. Yet here we have a chance to erase two thirds of this distressing health problem through controlled water fluoridation — a preventive measure that is simple and amazingly inexpensive.

Unless we do adopt fluoridation, widely and without delay, it is safe to predict that this whole generation of children will have lost half their teeth by the time they are forty years old. We can prevent this prediction from ever coming true if we refuse to submit to the fearful and misinformed attitudes of

a very few persons. We can avert this national tragedy if we insist on knowing the facts and if we insist on giving the privilege of better teeth to our children and our grandchildren.

Massachusetts has long been a leader in the field of public health. In 1678, the selectmen of Salem passed one of the first laws designed to prevent the spread of communicable disease.[1] Your State Health Department was the first to be established in the United States.[1] Furthermore, the whole foundation for promoting interest in sanitation and the prevention of disease in this country was laid by Lemuel Shattuck when he published the report of the Sanitary Commission of Massachusetts more than 100 years ago.[1]

Therefore, it is my hope and my belief that in respect to fluoridation, one of the latest and most effective of all public-health measures, Massachusetts will want to lead the way again.

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MEDICAL INTELLIGENCE

VOLVULUS AND PREGNANCY

A Case Report with Recommendations for Surgical Management

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VOLVULUS is a rare complication of pregnancy, only 9 such cases having been reported in the North American literature and only 85 having been found in the world literature through 1950. The following case of sigmoid volvulus complicating pregnancy is presented because of the relative rarity of the condition and because the successful outcome of this case, with survival of both mother and infant, makes the surgical principles involved worthy of discussion.

FIGURE 1. *Roentgenogram of the Abdomen (Supine), Showing Marked Distention of Large-Bowel Loops in Upper Abdomen. The fetus can be seen, with head lying in the pelvis.*

CASE REPORT

B. C., a 24-year-old primipara, was admitted on May 21, 1948, to the Columbia Presbyterian Medical Center complaining of lower-abdominal pain of five hours' duration. She had been followed in the Antepartum Clinic of the Sloane Hospital for Women, where, on December 23, 1947, a routine fluororoentgenogram of her chest revealed an incidental finding of a redundant colon interposed between the left lobe of the liver and the diaphragm. Aside from a life-long history of constipation there was nothing else of significance in her past history. Five hours before admission, in the 8th month of her pregnancy, she suddenly developed severe, steady lower-abdominal pain radiating to the lumbosacral area, felt weak and vomited three times. She was admitted to the hospital by her local physician with a diagnosis of onset of labor. The blood pressure was 124/80, the temperature 98.6°F. and the pulse 88. She was in acute abdominal distress, writhing periodically, and was restless and complaining. Her abdomen was distended, with a large tympanitic bulge extending from the xiphoid to the left flank, over which peristaltic waves could be seen to pass. No bowel sounds were heard. The fetal heart was audible and the fetus active. On pelvic examination the cervix was long and closed and the fetal head ballottable. There was no rectal tenderness. Three-position x-ray films of the abdomen revealed enormous distention of the large bowel (Fig. 1). The white-cell count was 20,000, with 82 per cent neutrophils. After a short period of unsuccessful attempts to deflate the bowel with colonic lavage, an exploratory laparotomy was performed under ether anesthesia with the presumptive diagnosis of volvulus of the colon. A long, high right-rectus incision was employed. A large, bulging loop of blue-tinged, thin-walled nongangrenous sigmoid appeared at once. A soft-twisted pedicle could be felt in the region of the left pelvic brim. The operator deflated the tense trapped loop of bowel with a large-bore needle, permitting easy detorsion of the loop with no trauma to the uterus. Normal bowel color appeared at once, and the colotomy site was closed. A large soft-walled rubber tube was inserted into the ascending colon by the Witzel technic, and the abdomen was closed. On the 5th postoperative day the patient was delivered by low forceps of a 2.2-kg. infant after a 3-hour labor. Twenty-five days after delivery she was again operated on for an elective resection of the sigmoid colon after a bowel preparation with sulfathalidine; an end-to-end anastomosis was performed. The patient was discharged on the 17th postoperative day and has been well ever since. Follow-up visits through February, 1950, have revealed both to be well.

DISCUSSION

The treatment of volvulus during pregnancy must be surgical if detorsion cannot be accomplished by means of rectal treatments. For a more detailed discussion of this condition the reader is referred to the article by Kohn and others.* Their patient had a volvulus untwisted surgically in the twenty-fourth week of pregnancy and went on to a normal delivery. Two years later this same patient, during her next pregnancy, was operated on for detorsion of volvulus in the twenty-eighth week and again in the thirty-sixth week. She delivered a child and five weeks after delivery again developed a volvulus, which was corrected by a Mikulicz type of resection.

The surgical management of the case presented here deserves emphasis for the following reasons: the decision for early operation after failure of detorsion from below, ignoring in effect the state of the pregnancy to treat the acute surgical problem;

*Kohn, S. G., Briele, H. A., and Douglass, L. H. Volvulus complicating pregnancy. *Am. J. Obst. & Gynec.* 48:398-404, 1944.

the use of a large incision to obtain adequate exposure with care taken to close the wound securely; the use of a colotomy on the trapped loop for deflation to avoid unnecessary manipulation and rupture of the bowel, and to facilitate detorsion; the use of a proximal vent colostomy situated high in the abdomen to keep the bowel deflated and to prevent recurrence of the volvulus during the remainder of the pregnancy and in the post-partum period; and the decision to resect the redundant loop of bowel in the early post-partum period, utilizing the colostomy already present, to avoid any further possibility of recurrent volvulus. In all cases a large rectal tube should be inserted into the rectum preoperatively, should detorsion be a relatively simple matter. In the more advanced cases, obstructive resection and cesarean section may be necessary. That the prognosis for both mother and infant is increasingly unfavorable under these latter conditions is obvious.

Summary and Conclusion

A case of pregnancy in the thirty-second week complicated by volvulus has been presented. The surgical principles found of value in the successful outcome of this case have been discussed.

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 38191

Presentation of Case

A forty-one-year-old woman was admitted to the hospital because of chest pain and dyspnea.

Three months prior to entry, while doing some heavy lifting, she noted a sharp pain on the right side of the neck and shoulder. The pain persisted during the remainder of that day but was not severe enough to make her stop work. This recurred subsequently as a fleeting sharp pain in this area. At about the same time she first became conscious of shortness of breath on relatively mild exertion; this remained unchanged until two weeks prior to entry. About two months prior to entry she developed a sharp pain in the right axilla that was made worse by deep breathing and that persisted for a number of hours; during this episode she coughed up approximately one-half teaspoonful of bright-red blood. This pain recurred infrequently over the next six weeks; on most days it was mild, but on the others it was severe and was aggravated by respiration. One month prior to entry she again coughed up a small amount of bright-red blood. Two weeks prior to entry the pain settled in the right posterolateral chest and became more severe and steady; it was aggravated by coughing, lying on the right side or deep respiration. She felt alternately chilly and warm, had a cough that was productive of a slight amount of whitish-yellow, sometimes slightly blood-tinged sputum, had increased dyspnea and developed mild orthopnea. Her physician found that she had a temperature of 100°F. and made a diagnosis of pneumonia and pleurisy. She received one intramuscular injection of penicillin, which was followed by oral penicillin for five days. On the third day of this treatment she developed a pruritic red rash in both axilla and groin and on the last day of treatment a numbness in the right buttock and pain in the posterior aspect of the right thigh and knee; both these symptoms improved spontaneously. By the end of this treatment, four days before admission, she felt somewhat improved. However, on the following day there was a recurrence of all the symptoms; the pain was less severe, but the shortness of breath and the cough was more severe.

She had had marked anorexia for two weeks and thought that she had lost several pounds in weight. There had been no recent upper-respiratory infections or sore throats, no wheezing and no ankle or abdominal swelling. Eight years before admission she had been given iodine therapy for an undetermined length of time because of a "thyroid" condition. She worked as a clerk in a tailor shop and had continued to work until ten days before admission.

Physical examination revealed a well nourished woman who had mild dyspnea while lying at a sixty-degree angle. She complained of mild right-chest pain. There was no cyanosis. The thyroid gland was 1.5 times normal in size. The veins in the neck were full but not pulsating. The trachea was in the midline. The breasts were normal. There was a faint reddish-brown maculopapular rash in the axillas and on the forearms. There was dullness to percussion in the right lower chest posteriorly and in the axilla, with decreased breath sounds, and decreased vocal and absent tactile fremitus in this region; above the level of the dullness posteriorly and in the anterior right chest a few rales were heard.

The left chest was normal. The heart was not enlarged and there was no arrhythmia or murmurs; the pulmonic second sound was equal to or slightly louder than the aortic. The abdomen was negative. There was no clubbing or edema of the extremities. The dorsalis-pedis pulsations were normal.

The temperature was 101.8°F., the pulse 120 and the respirations 34. The blood pressure was 130 systolic, 90 diastolic.

A urine of specific gravity 1.009 was normal. Examination of the blood showed a hemoglobin of

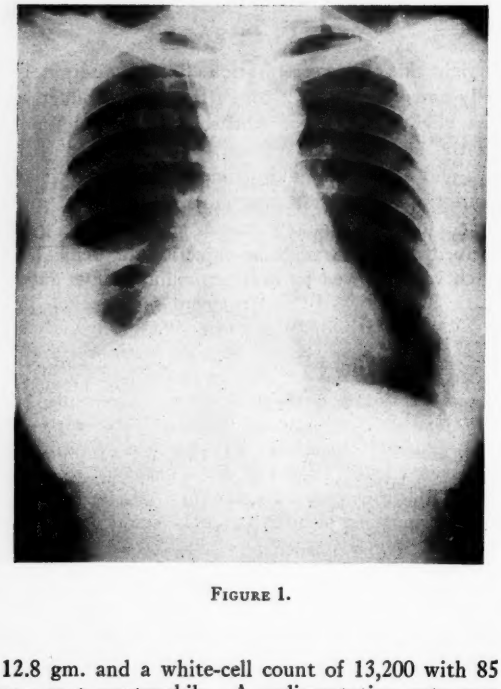

FIGURE 1.

12.8 gm. and a white-cell count of 13,200 with 85 per cent neutrophils. A sedimentation rate was 50 mm. per minute (uncorrected). A circulation time (arm to tongue) was 20 seconds. Roentgenograms of the chest showed fluid in the right pleural cavity, with considerable reduction in the size of the right lower lobe and some reduction in size of the right middle lobe (Fig. 1). The left lung, heart and aorta were not unusual. Thoracentesis above the eighth right rib posteriorly in the posterior axillary line yielded 300 cc. of fluid that was at first cloudy yellow with a faint pink tinge and then grossly bloody; the fluid did not clot, had a specific gravity of 1.016 and contained 7.6 mg. of protein per 100 cc., 1350 large mononuclear cells and 1875 small mononuclear cells per cu. mm.

After admission she was acutely ill, the dyspnea increased and she was very apprehensive. On the second hospital day three hours after the thoracentesis she began to have much more respiratory distress, became markedly cyanotic and complained of right-anterior-chest pain and pain along the left costal margin and of difficulty in breathing. The respirations were 44 and deep, the temperature 96°F. and the pulse 140 and weak; the blood pressure was unobtainable. The neck veins were distended and tense, the trachea was shifted to the left and although the chest excursions were equal bilaterally the breath sounds were slightly diminished over the entire chest, most markedly over the right base. A roentgenogram of the chest showed a moderate-sized right pneumothorax, a large area of density in the lateral basal segment of the right lower lobe and an area of density adjacent to the right heart (Fig. 1). The azygos vein was considerably distended. A white-cell count was 23,800, with 88 per cent neutrophils and a hemoglobin of 11 gm. An electrocardiogram showed a sinus tachycardia of 140, a PR interval of 0.10 second and a QRS interval of 0.07 second, and S waves were present in Lead 1; the Q waves were present in Lead 3 and small in Lead AVF; the T waves were inverted in Leads 3, AVF, V_1 and V_2 and upright in Leads V_4, V_5 and V_6. There was a clockwise rotation. She was given oxygen by mask and a blood transfusion. The respirations continued to be rapid and the blood pressure was unobtainable. She died late on the afternoon of the second day.

DIFFERENTIAL DIAGNOSIS

DR. ALLEN G. BRAILEY*: May I see the x-ray films?

DR. STANLEY M. WYMAN: The original interpretation on these films was that the density seen in the right chest laterally and anteriorly in the region of the heart border was due to fluid; the density was later interpreted as being in the lung itself, out against the pleural surface and extending into the lung for some distance. These densities are present in the lateral segment of the right lower lobe and in the middle lobe (Fig. 1). The peripheral lung fields are unusually bright and the vascular markings are somewhat diminished. The heart shadow itself is not remarkable. The films taken the next day in bed show marginal pneumothorax in the right chest and demonstrate clearly that this density, which was originally thought to be in the pleural space, actually lies in the lung itself. The density in the right middle lobe is well seen in these films.

DR. BRAILEY: Is there anything unusual about the pulmonary artery in the second film?

DR. WYMAN: I think it is a little difficult to be sure in this film. The peripheral vessels are, I think, less well seen than usual. Perhaps the central vessels are slightly more prominent.

DR. BRAILEY: Is it fair to ask you what you would call this mass in the base of the right lobe?

DR. WYMAN: Probably infarcts.

*Assistant physician, Massachusetts General Hospital.

DR. BRAILEY: You ruled out tumor?

DR. WYMAN: I think the multiplicity, the shape and the location of the densities is in favor of infarcts.

DR. BRAILEY: I have several thoughts in mind on reading this protocol. In the first place, this woman seems not to have had the habit of asking for or receiving very thoughtful medical care. There was the report that for a while at the age of 33 she had had iodine therapy for a "thyroid condition." Nothing is said about the symptoms that she had at that time, but one wonders whether she was given this iodine simply because she had a palpable thyroid. Of course, during the times of unusual thyroxin demands, such as adolescence and pregnancy, modest doses of iodine may prevent the development of hypertrophy, but it seems likely that this woman's tiny goiter was due to previous, not to any current, demands; hence iodine therapy could not have been expected to do any good.

The symptoms that finally brought her to the hospital began three months before entry; nevertheless, she worked until ten days before entry and apparently did not see a physician until about that time; the physician decided that she had pneumonia; that also seems a little disappointing. She told the physician, or at least she could have told him, that she had had pleuritic pain for three months and shortness of breath for about the same period. Pneumonia, at least of the usual type, does not seem a likely explanation for this sequence of events. Apparently she did not have continuous pleural pain but had repeated exacerbations, with pain sometimes in one place and sometimes in another, although it was usually confined to the right chest. A very important symptom is that she coughed up some blood. It is true that apparently healthy people may from time to time raise a mouthful of bright-red blood for which no source is ever found and that must be presumed to be due to the rupture of a small varix; however, hemoptysis must always be regarded as a significant and ominous symptom until it is proved otherwise.

Then there was also gross blood in the pleural-effusion fluid that was removed. That one piece of evidence rather sharply narrows the diagnostic field. A bloody pleural effusion implies trauma, an acute inflammatory process, tuberculosis (although tuberculous fluid is rarely frankly bloody), invasion by tumor or infarction of the subjacent lung. It seems rather easy to dispose of infection in this situation. The clinical course was too long and too slowly progressive for the usual pyogenic infection; the pleural fluid that was withdrawn was not consistent with an exudate of a pyogenic infection; in fact, I am rather amazed to be told that it contained no polymorphonuclear leukocytes at all. On the other hand, tuberculosis ought not to be so easily tossed aside; it would explain the protracted course, the persistent or recurrent pleural pain, the cough, the fever and the loss of weight. The characteristics of the pleural fluid were not inconsistent with those of tuberculous fluid. Tuberculosis, however, would seem rather unlikely as an explanation for the severe dyspnea, the distended neck veins, the rapid pulse and the manner of her demise. Then, of course, the appearance of the x-ray films is certainly not suggestive of tuberculosis, but it does not rule out a tuberculous pleurisy by any means.

Could this woman have had neoplastic disease? Cancer of the bronchus that had extended or metastasized to the pleura might have produced these signs and symptoms and, by invasion of the periarterial lymph nodes or compression of the pulmonary veins, might have produced the cor pulmonale that I think ended her life — but the x-ray studies again give no evidence of any such widespread or strategically placed neoplasm.

It seems to me that the condition that offers the most logical explanation of the clinical course and symptoms is multiple embolization of the pulmonary arterial tree. Emboli caused multiple infarctions of the lungs, with subsequent bloody effusions; emboli cut down the pulmonary arterial bed with gradual production of pulmonary heart disease. The actual *coup de grâce* may have been the development of the pneumothorax after the tap. I wonder if an effort was made to reduce the pneumothorax; it seems to me that it would be useful. Were anticoagulants used? Perhaps it was already too late for them to have been lifesaving, or perhaps this was another case in which anticoagulants failed the physician. The source of the emboli may have been the right heart chambers. I even toyed briefly with the thought that she might have had subacute bacterial endocarditis, but she had no heart murmur and the emboli were apparently not septic.

Can I be satisfied that she died of embolism and nothing else? Three hours after the chest tap, she developed acute circulatory failure and went into a state of shock from which she never rallied. The electrocardiogram, which Dr. Ernest M. Craige was good enough to review with me, suggests right-heart strain with changes that are consistent with acute cor pulmonale, but it is not inconsistent with posterior infarction. Perhaps she had an occlusion of the right coronary artery of the usual atheromatous sort to add further insult to her already serious injuries. On the other hand, if she had progressive obstruction of the pulmonary circulation, one might expect that the cardiac output would tend to fall. Cournand,[1] who has made a study of pulmonary circulation, found that the cardiac output does not fall in cor pulmonale. Actually, it tends to rise, because the blood volume also rises. That is not surprising, as what goes into the right heart must come out through the left sooner or later as long as compensation exists; cardiac output will be maintained until compensation finally fails — but when compensation fails, the blood pressure will prob-

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ably drop precipitously and nutrition of tissue in general and of the heart muscle will be quickly impaired. I think it is likely that this heart showed histologic evidence of infarction but no occlusion of the coronary tree. I was interested to find that Dack and his associates[2] had reported cases of cor pulmonale with exactly this series of events and with cardiac infarction for which there was no obstruction to offer an explanation.

In passing, I wonder if transfusion was an entirely rational treatment; if the blood was piling up behind the pulmonary obstruction, it seems unlikely that increasing either the blood volume or the hemoglobin would help her appreciably.

I think the patient had multiple pulmonary emboli with cor pulmonale and possible cardiac infarction.

DR. ROBERT L. BERG: I followed the patient for about five hours prior to her death. When I first saw her three hours after the chest tap, her condition was obviously bad. We believed at that time that there was a considerable disproportion between the dyspnea and the x-ray report of nothing more than pleural fluid. Then it appeared that she might have suffered a pneumothorax that was interfering with her respirations, but when the films showed such a small pneumothorax it did not seem likely that that would account for the whole condition. At this point Dr. Churchill was asked to see her.

DR. EDWARD D. CHURCHILL: The clinical diagnosis was fairly straightforward, except for certain "red herrings," which are always present in a seriously ill patient. The concern at the time I saw her centered on the chest tap and the small pneumothorax induced by it. A patient can withstand a marginal pneumothorax without being aware of it, so it was not taken very seriously as a precipitating factor in this woman, who was ventilating both lungs adequately. My first impression was that she was hysterical and hyperventilating as a result, but physical findings were not compatible with this explanation. She had a very feeble pulse and no measurable systolic blood pressure. The fact that cyanosis was recorded in the abstract is of interest. I would not have classified her as a deeply cyanotic patient insofar as there was any evidence that the small amount of blood in the arterial circulation was inadequately oxygenated. Her fingernails were not discolored or cyanotic. The striking physical finding was distended, tense neck veins. It had been noticed on admission to the hospital that she had distended neck veins, and I cannot compare the distention on admission with the distention I observed. To me, the veins looked very distended and tense. The blood was backed up on the venous side, but the little that was flowing through the heart and lungs was being oxygenated.

A patient with thrombophlebitis is, of course, likely to have an acute pulmonary embolism; hers came on after her chest tap but was related only incidentally to the chest tap. With this type of pulmonary embolism the patient can live for a matter of hours, sometimes 13 or 15 hours, and will die as a result of the totally inadequate output from the left side of the heart, exactly as a person dies of acute hemorrhage. The surest way to distinguish such a picture from that of continuing internal hemorrhage is the visible distention of the cervical veins. In the left side of the circulation this patient showed lack of blood volume; in the right side, blood was backed up by the embolus lodged in the pulmonary artery.

I do not know why Dr. Wyman was trying so hard to demonstrate that the pulmonary vessels were poorly filled at the time of admission. I would expect that elsewhere than in the infarct they would be normal. The blocking of the pulmonary circuit came later. At that time, after the final embolism, the pulmonary vessels might have been poorly filled.

DR. BRAILEY: Don't you think, Dr. Churchill, that she had a considerable blockage of the pulmonary circuit long before she came to the hospital?

DR. CHURCHILL: No; I think the first emboli lodged in the periphery of the lung. You probably would not have found even an increase in pulmonary pressure from the few infarcts.

DR. BRAILEY: Why was she so short of breath, and why was the pulse so rapid?

DR. CHURCHILL: I think the shortness of breath was much more likely to have been of neurogenic origin from multiple peripheral infarcts.

DR. WYMAN: It was only after we had reviewed this case in great detail that we were aware of the changes in the periphery of the lungs, which I think are fairly valid. These changes, — the avascular peripheral lungs and possibly some increased prominence in the central hilar vascular shadows, — I think were of some duration before she was seen here.

DR. CHURCHILL: Well, why wouldn't blocking of some vessels in the right lung cause more blood to flow through the left lung?

DR. WYMAN: I think there was a block in the left lung, too.

DR. CHURCHILL: Without hemorrhagic infarction?

DR. WYMAN: That is correct — in other words, thrombosis.

DR. CHURCHILL: You are postulating a slowly extending pulmonary-artery thrombosis?

DR. WYMAN: Starting on emboli.

DR. BENJAMIN CASTLEMAN: Dr. Maloof, have you any comment?

DR. FARAHE MALOOF: My only comment would be made in retrospect, as we did not think of this syndrome until Dr. Churchill brought it to our attention. On looking up these cases, apparently the dyspnea, far out of proportion to anything in the heart or lungs, is one of the most characteristic findings; the distended neck veins and the marked apprehension mentioned by Dr. Churchill are sup-

posedly characteristic manifestations. Exophthalmos, suffusion of the face and other findings have been described, but those three symptoms and signs are supposed to be characteristic.

DR. ARTHUR S. PIER: Would you consider an embolectomy here?

DR. CHURCHILL: We considered it but did not attempt it.

CLINICAL DIAGNOSIS

Pulmonary embolism.

DR. BRAILEY'S DIAGNOSES

Multiple pulmonary emboli.
Cor pulmonale.
Cardiac infarction.

ANATOMICAL DIAGNOSES

Pulmonary embolism, massive, bilateral.
Thrombosis of leg and common femoral veins, bilateral, and inferior vena cava.
Pulmonary infarct, right lower lobe.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: Both main pulmonary arteries and their branches contained emboli that were adherent to their walls. This was especially marked in the vessel to the right lower lobe, where the embolus was gray and much more adherent. In the inferior vena cava was a huge mural thrombus that extended from the left common femoral vein, which in turn came from the leg veins that were entirely thrombosed on the left side. There was also thrombosis of the popliteal and calf veins on the right side. Thus, the source of the emboli was easily established. There was a large infarction in the right lower lobe, 10 by 9 cm., as you saw in the x-ray film, and one also in the right middle lobe. The right upper lobe and the two lobes on the left showed no evidence of infarction. We have now seen enough of these cases to know that had this patient lived she would have developed cor pulmonale. Some patients have lived for many years, but most of them develop right-heart failure and die in about two years.

The heart was normal in size, with slight dilatation of the right chamber and no evidence of myocardial infarction. The coronary arteries were normal, and the heart muscle showed no evidence of anoxia in a few random sections.

DR. BRAILEY: Would you expect to find any in so short a time?

DR. CASTLEMAN: No; it is about 12 hours before real evidence of any change in the heart appears.

DR. CHURCHILL: Do you think the final straw in shutting off the pulmonary circulation was a new embolus coming from the periphery, or do you think it was a thrombus from the preceding embolus?

DR. CASTLEMAN: I think it was another embolus.

DR. BRAILEY: Might it be that she was in such a critical stage that the pneumothorax was just enough to tip the scale?

DR. CHURCHILL: I do not believe a pneumothorax of that size would interfere materially with the circulation. It certainly wouldn't interfere with the ventilation.

DR. BRAILEY: Except in a person whose pulmonary circulation is barely adequate!

DR. EDGAR A. TAFT: How often do you see massive peripheral thrombosis without any peripheral edema?

DR. CASTLEMAN: I would have expected some.

DR. CHURCHILL: That was one of the "red herrings."

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CASE 38192

PRESENTATION OF CASE

First admission. A forty-five-year-old woman entered the hospital because of abdominal swelling.

The patient had been known to have an enlarged spleen and anemia for twenty-five years; fifteen years prior to admission esophageal varicosities had been demonstrated roentgenographically. Eleven years prior to entry during hospitalization for teeth extraction the following were noted: The spleen was greatly enlarged, extending to 2 cm. below the umbilicus; the hemoglobin was 13.2 gm. and a white-cell count 4700; examination of a blood smear showed normochromic normocytic red cells, and the platelets appeared to be decreased in number; the bleeding time was nine minutes and the clotting time ten to sixteen minutes. The teeth extraction was without incident. Iron therapy had apparently maintained her hemoglobin within normal limits, and the patient had no particular discomfort for over ten years. Six months prior to admission she first noted swelling of the ankles toward the end of the day that subsided by the next morning. After three injections of Mercuhydrin the swelling no longer occurred until one month prior to admission. One week prior to entry she noticed a marked increase in the size of the abdomen, which felt full. Shortly after this she had a slight chill and ached "all over" for several days. There had been a weight gain of fifteen pounds in the few months before admission.

Her appetite had always been good. There had been no hematemesis, jaundice, clay-colored or tarry stools, abdominal pain, dyspnea or urinary symptoms. There was no history of alcohol consumption. She had had no known serious illnesses in the past. She had had two normal pregnancies.

Physical examination revealed a well developed, well nourished adult woman in no acute distress. The scleras were slightly icteric. The skin was normal. There were a few petechial hemorrhages on

the hard palate. The left diaphragm was high but descended with inspiration. There was a Grade II apical systolic murmur. The abdomen was enlarged and contained a slightly tender mass that occupied the entire left upper quadrant from the xiphoid to the umbilicus. The liver was not palpable. There was ++ pitting edema of the ankles.

The temperature was 98.6°F., the pulse 80 and the respirations 22. The blood pressure was 140 systolic, 80 diastolic.

The urine had a specific gravity of 1.012 and gave a ++ reaction for albumin and a negative reaction for bile. On examination of the blood the bilirubin was 3.7 mg. direct and 5.9 mg. total, the total protein 3.85 gm., the albumin 2.21 gm. and the globulin 1.64 gm. per 100 cc.; the cephalin flocculation was ++++ in twenty-four hours. Stool examination showed a normal brown color and a negative guaiac reaction. A barium-swallow examination showed slight widening of the lower esophagus and tortuosity and prominence of the mucosal folds. There was a small hiatus hernia and the stomach was displaced far toward the midline. A roentgenogram of the abdomen showed the spleen to be greatly enlarged, extending to about 5 cm. above the iliac crest. There was one area of calcification overlying the first lumbar vertebra and a second area superimposed on the left eleventh rib. The hepatic flexure lay unusually high, but the liver could not be definitely outlined. There was fullness of the left paraspinal shadow in the lower thoracic region, and the abdominal visceral outlines were slightly less well visualized than usual.

She was placed on a low-salt diet and given ammonium chloride and Mercuhydrin. She had a good diuresis, losing six pounds in weight, and was discharged on the third day.

Second admission (three weeks later). In the interval the patient did well until ten days prior to entry, when she became confused and disoriented. The following day, when she was admitted to another hospital, she was amnesic, lethargic and jaundiced and had an icteric index of 39. She was given two blood transfusions, following the latter of which she had a slight chill and vomited; the urinary output and icteric index remained unchanged. Her mental state cleared three days before admission, although she was unable to recall the foregoing episode. The abdominal enlargement had remained, but the ankle edema had regressed in the three-week interval.

On physical examination the protuberant abdomen now had a fluid wave and was positive for shifting dullness. The spleen was unchanged from the previous admission and the liver could not be felt. There was + pitting edema of the ankles.

The temperature was 99°F., the pulse 82 and the respirations 22. The blood pressure was 130 systolic, 70 diastolic.

Examination of the blood showed a hemoglobin of 11.8 gm. and a white-cell count of 7500, with 84 per cent neutrophils; a blood smear showed 1 myelocyte and 4 late myelocytes, normal platelets, polychromasia and + variation in size of the red cells, which were slightly smaller in size than normal and were occasionally elongated, tailed and bizarrely shaped. The bilirubin was 6.8 mg. direct and 11.4 mg. total, the nonprotein nitrogen 23 mg., the total protein 3.68 gm., the albumin 2.25 gm., the globulin 1.39 gm., the fasting blood sugar 73 mg. and the serum alkaline phosphatase 3.0 units per 100 cc. The sodium was 134.2 milliequiv., the potassium 4.4 milliequiv. and the chloride 110 milliequiv. per liter. The cephalin flocculation was +++ in twenty-four hours and ++++ in forty-eight hours, the bromsulfalein showed 50 per cent retention in the serum and the prothrombin time was 18 seconds (normal, 14 seconds). The urine had a specific gravity of 1.010 and gave a + reaction for albumin and a ++ reaction for bile. A two-hour urine specimen for urobilinogen contained 57.5 Ehrlich units and a semiquantitative determination for urobilinogen in the stools showed 528.0 Ehrlich units per 100 gm. A Coombs test was negative. A stool guaiac test was negative. Roentgenograms of the chest showed clear lung fields; the diaphragms were rather high bilaterally, the heart was in a transverse position and a small area of homogeneous density was noted in the left costophrenic angle. An electrocardiogram was normal.

The patient was given 2 blood transfusions and intravenous albumin and dextrose but her condition became progressively worse; jaundice, spider angiomas and sacral edema were noted and the ascites remained unchanged. The hemoglobin was 10.3 gm. on the tenth day and 7.8 gm. on the fourteenth. On the tenth day the reticulocyte count was 4.5 per cent and the stool urobilinogen 417 Ehrlich units per 100 gm. On the twelfth day she developed a low-grade fever up to 101°F., which responded to aureomycin, and then nausea and vomiting, which responded to atropine. She became a little drowsy,

especially in the evenings; the jaundice was unchanged, but the edema and the ascites were less marked. On the fifteenth day the bilirubin was 8.5 mg. direct and 14 mg. per 100 cc. total, the stool urobilinogen 122 Ehrlich units per 100 gm., the serum protein 4.82 gm. per 100 cc., with an albumin-globulin ratio of 2.1, and the nonprotein nitrogen 23 mg. per 100 cc.; the serum sodium was 141.6 milliequiv. and the serum chloride 108 milliequiv. per liter. On the nineteenth day cortisone therapy was begun. Over the next four days there were certain signs of improvement; a slight lessening of the jaundice, disappearance of most of the edema and ascites and a better caloric intake. Then, however, the patient became disoriented and confused and the drug had to be stopped. On the twentieth day the hemoglobin was 9.4 gm., the red-cell count 2,530,000, the reticulocyte count 7.2 per cent and the bilirubin 8.1 mg. direct and 13.2 mg. total per 100 cc. On the twenty-third day the hemoglobin was 8.7 gm., the reticulocyte count 13.1 per cent, the urine urobilinogen 1.2 Ehrlich units and the stool urobilinogen 112 Ehrlich units per 100 gm. From the twenty-fourth day on she was comatose; ascites was no longer clinically detectable and the edema was minimal. The temperature, pulse and respirations became elevated; she developed coarse rales throughout the chest, became oliguric and died on the thirty-third day, after a twelve-hour period during which her temperature ranged between 105 and 108°F.

Differential Diagnosis

Dr. Bernard M. Jacobson*: I believe that in the diagnosis of this patient's fundamental illness the history is of the utmost importance and that not much useful information was added by the physical examination and hospital course.

What could this have been? The patient was quite well, although she had, for at least 25 years, a markedly enlarged spleen and probably intermittent anemia that had responded to iron administration and for about 15 years portal hypertension as shown by esophageal varicosities. There are not many conditions that can last this long. Certainly congenital hemolytic jaundice would be unlikely to present a spleen this large, and there was no history of jaundice. Infiltrative lesions of the spleen such as Gaucher's disease would be extremely unlikely because of the duration. Postinfectious splenomegaly of this sort following such diseases as malaria or typhoid fever would also be extremely unlikely. Could this have been a malignant tumor such as myelogenous leukemia or malignant lymphoma of 25 years' duration? I doubt it. Could this have been the rare case of myeloid metaplasia of 25 years' duration? I shall certainly discard that. Thus I am left with very few possibilities.

It seems to me that the most likely diagnosis is probably some form of primary splenic fibrosis; as Eppinger[1] called it, hepatolienal fibrosis, or, as it is now classified, congestive splenomegaly. You will note that I am trying not to mention the term "Banti's syndrome," yet we cannot get away from it. In spite of Banti's changing his mind in many of his papers, he did factually describe cases that certainly would include this patient — a woman with splenomegaly of unknown origin starting at least at the age of 20. At that time she would have been in Banti's anemic phase: splenomegaly, at times anemia, at times leukopenia, at times hemorrhagic episodes, usually lasting for years. The esophageal varicosities — apparently without evidence of liver disease at the time — make it likely that the portal hypertension was of extrahepatic origin, which would fit with this syndrome. After 25 years, six months prior to entry, the patient entered Banti's ascitic stage, with liver atrophy and cirrhosis — a terminal stage. Nothing in this patient's later course leads me to any conclusion other than that this was a case of idiopathic hepatolienal fibrosis, with the development of cirrhosis and all the consequences of liver failure.

May I see the x-ray films? Were the original films taken in this hospital?

Dr. Joseph Hanelin: No; the only ones we have are relatively recent.

The spleen, which is greatly enlarged, occupies most of the left abdomen. The liver, although not sharply delineated, appears smaller than normal, as indicated by the crowding of bowel loops in the right upper abdomen. There is also evidence of increased intra-abdominal fluid. The barium-swallow examination shows the presence of wide folds in the lower esophagus that appear to represent moderate-sized varices. On the second admission, the chest examination is not remarkable except for a high diaphragm, which can be accounted for by the intra-abdominal change. There is a zone of density at the left base far posteriorly, which could represent a lesion such as an infarct.

*Assistant physician, Massachusetts General Hospital.

DR. JACOBSON: I have based my diagnoses on the patient's history up to the time of the first admission; however, I should like to comment on a few of the findings made during the two admissions. I assume that the negative reaction for bile reported during the first admission was an error, as a good deal of bile was present later. The bilirubin content of the blood at that time indicated diffuse disturbance of the liver and liver-cell disease.

During the second admission, the ++ reaction for bile in the urine proves that the jaundice the patient had at that time was not hemolytic but was due to liver damage. I am surprised that the alkaline phosphatase was low normal, in the presence of so much liver disease. The change in the size and shape of the red blood cells during the final admission also may have been due to hepatic failure, although it may have been due in part to oozing from the esophageal varices and possibly to malnutrition. Interpreting a 4.5 per cent reticulocyte count at the terminal stage of an illness is difficult. It may have been the response of a fairly healthy bone marrow to bleeding, or it may have been due to a low-grade hemolytic process.

Why was cortisone used? I wonder whether the physicians had accumulated better evidence than we are given of acquired hemolytic anemia. At any rate, it is difficult to believe that the urinary urobilinogen was decreased to the degree that it was, as an effect of cortisone in the presence of acquired hemolytic anemia, without a corresponding drop in the bilirubin. That the serum bilirubin was still 8.1 mg. direct and 13.2 mg. total per 100 cc. suggests that a good part of the jaundice was due to hepatic disease, and that possibly a good part of the urobilinogenemia was due to acquired hemolytic anemia.

I think that these speculations on this subject may be the end of the story, because I doubt whether the pathologist can tell us at autopsy whether the patient had hemolytic anemia during life. Despite the negative Coombs test, acquired hemolytic anemia can explain this drop in urinary and fecal urobilinogen under the influence of cortisone. To go back to the differential diagnoses in the outset of my discussion, I have nothing further to add, except possibly terminal hemolytic anemia.

DR. PERRY CULVER: Number one: I should like to know why Dr. Jacobson wants to put the changes in the spleen before those in the liver rather than the liver before the spleen?

Two: I should like to know if he has any idea of how long liver disease may be present and not be recognized?

Three: I am of the Thorndike school, believing that urine urobilinogen is not elevated in hemolytic jaundice alone but that there must be an element of liver disturbance along with increased hemolysis to give elevated urine urobilinogen, in which case a stool urobilinogen is of some value in helping one to decide whether there is increased hemolysis or not. Some, particularly Cecil Watson, take exception to that point of view. There has been a running fight for a number of years between those two groups.

Four: Although the test that we make here for stool urobilinogen is at best semiquantitative, it does indicate a definite increase in urobilinogen in the stool. In several recent cases there has been chronic liver disease, some evidence of increased hemolysis and an increased stool urobilinogen. I am not yet quite sure of the significance of the whole picture.

Dr. Chester Jones, who insisted on giving cortisone, is not here to defend his position. He gave it with caution after a great deal of discussion. He thought that there was enough evidence on the basis of the stool urobilinogen to justify the probable diagnosis of acquired hemolytic anemia and that, inasmuch as the patient was not getting better and the anemia was so severe that a splenectomy and shunt operation could not be considered, cortisone was the only thing that could possibly aid the patient.

Some of us thought that this patient's disorientation was due not to cortisone but to liver failure.

Why did the urine urobilinogen drop to 1.2 units and the stool urobilinogen also drop? I think I agree that it was due to decrease in hemolysis, but if there was this much liver damage, the urine urobilinogen should have remained elevated. I do not believe, however, that one should put much emphasis on a single laboratory test.

DR. JACOBSON: First — the question of urine urobilinogen. It is fairly definite that in the last five or six patients with acquired hemolytic anemia of unknown cause and with intact liver function the urinary urobilinogen was constantly elevated; therefore, the urinary urobilinogen is of value in those patients as evidence of increased hemolytic activity.

DR. CULVER: But there is impaired liver function secondary to anemia.

DR. JACOBSON: Judged by ordinary liver-function tests, I mean. If one has to be in one school or another, I shall be in Dr. Watson's school. I shall leave untouched the question of these fecal urobilinogen values.

"Why couldn't this have been liver disease from the beginning?" I think that if you and I had seen this patient 25 years previously we should have taken that spleen out before she developed liver disease, and we should have done a biopsy of the liver. We might have prevented the extrahepatic deterioration of the portal circulation and might have, as Banti said, cured the patient.

A PHYSICIAN: The patient was taking aureomycin for a number of days before her death. Could the change in the bacterial flora have had anything to do with the terminal reduction in fecal and urinary urobilinogen?

DR. CULVER: That could be another confusing factor. As I did not know the time relation between the aureomycin and urobilinogen determinations, I did not want to become involved in that discussion.

CLINICAL DIAGNOSIS

Hepatic failure.

DR. JACOBSON'S DIAGNOSES

Hepatolienal fibrosis.
Cirrhosis of liver, with functional failure.
?Terminal hemolytic anemia.

ANATOMICAL DIAGNOSES

Hepatic cirrhosis, postnecrotic type.
Fibrocongestive splenomegaly.
Esophageal varices.
Ascites.
Erythroid hyperplasia of bone marrow.
Hemosiderosis of pancreas, liver and kidney.
Bronchopneumonia.
Pulmonary congestion and edema.

PATHOLOGICAL DISCUSSION

DR. ROBERT E. SCULLY: At post-mortem examination the spleen was enormous, weighing 1400 gm.; the splenic vein was greatly dilated. There was no obstruction in the extrahepatic portal system; the liver, however, was quite small, weighing only 900 gm.; it presented the typical macroscopical features of so-called postnecrotic cirrhosis, which is characterized by regenerated nodules that vary considerably in size. In the portal vein was a thrombus of relatively insignificant size that seemed to be of no more than several weeks' duration at most.

Microscopically, the spleen showed the typical picture of fibrocongestive enlargement; there was no evidence of extramedullary hematopoiesis. The liver was cirrhotic; there was no recognizable evidence of acute liver-cell damage. The remainder of the findings were as one might expect: esophageal varices, ascites and erythroid hyperplasia of the bone marrow, chiefly at the normoblastic level. There was a fair amount of hemosiderin deposition in various organs — liver, pancreas and kidney; this may have been due at least in part to a hemolytic process. Terminally there were bronchopneumonia and pulmonary congestion and edema.

Although some authorities[2] in the field suspect that splenic involvement may precede hepatic cirrhosis in some cases of so-called Banti's syndrome, we believe that this case was most likely one of primary liver disease with secondary splenomegaly. Spleens of this magnitude are certainly the exception in postnecrotic cirrhosis, but we have seen them on several occasions. In one case discussed at a clinicopathological conference some fifteen years ago,[3] the patient, a thirty-five-year-old man, had suffered a clinically typical attack of infectious hepatitis at approximately the same time as his brother. The latter died shortly thereafter of subacute yellow atrophy; the former, however, lived for fourteen years and then finally died with postnecrotic cirrhosis, a spleen weighing 1000 gm. and esophageal varices. Thus this type of cirrhosis can apparently go on for a long time before decompensation sets in.

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EMERGENCY MATERNITY AND INFANT CARE

FAR from producing a demand for World War II's so-called EMIC system of care for the wives and families of servicemen, the March congressional hearings seem to have resulted in many objections from opponents of the bill and, to say the least, a lukewarm reception. According to report,[1] public attendance at the hearings was poor, and as for the subcommittee's own attendance, not one of its Republican members put in an appearance. Apparently chairman Herbert Lehman sat alone except for one or two mornings when Senator Lister Hill (D., Ala.) joined him.

Dr. Martha Eliot, chief of the Children's Bureau, has ably presented the case for S.1245 and S.2337;[2] but most physicians and apparently most of their patients regard as questionable the emergency character of the proposed legislation — questionable, at least, in comparison with the catastrophic, all-out cleavage of normal living that suddenly occurred on December 7, 1941. Dr. Eliot stressed the priority nature of adequate medical care for the wives of servicemen during maternity and for their babies and young children — especially for the mothers who may be far from home and friends at the time of an unexpected confinement. "It is a matter of the first importance that the man who is away from his family, serving his country, can be assured that during the time his wife is pregnant and his children are small, they will be able to get the care they need." All will agree with this, and it is official policy that dependents of servicemen are eligible for health and medical care from military personnel in military hospitals.

Some of Dr. Eliot's case against the "inequities of the present situation," however, is unconvincing. In the first place, she did not succeed in defining precisely what those inequities are in principle. Many of the facts presented were based on the use of questionnaires. Although such a procedure may provide useful information, the interpretation of data should be critical and not merely forensic. If "reports that have come to us" indicate that some servicemen "do not understand that such care is available only in military hospitals," this concerns not the merits or demerits of the system of medical care in use but rather its implementation.

That many men are anxious about how the bills will be paid when their wives are going to have a baby is quite understandable when one realizes that the wife of a man in any of the lowest three pay grades receives a monthly Government check for $85. Of itself, this is only an argument that the wife should be able to avail herself freely of high standard care at a service installation; as it stands, the fact is no argument for an EMIC.

The isolated case history is not effective and convincing evidence in favor of a bill that involves several hundred thousand families, especially when it seems to have been introduced for heart-string

appeal rather than to cope directly with the issues involved. "I can recall the case of a mother," testified Dr. Eliot, "who was dying from hemorrhage. A well qualified obstetrician was called in for consultation (under the World War II EMIC). Transfusions were given and other modern therapeutic measures followed. As a result her life was saved." The case cited seems a tribute more to modern obstetrics than to EMIC. Dr. Eliot described another case, a premature birth of twins. "The mother was in a small hospital which was not equipped to take care of premature infants. The babies were put into an incubator and taken to a larger hospital nearby. The needed medical care was provided and the lives of these babies who had come into the world weighing less than five pounds were saved." Is this case history any real evidence that the babies would have fared worse had there been no EMIC or had the babies been born to the same couple in civilian life?

At present only a slim chance is seen for enactment; that would depend on a major increase in the size of the Armed Forces. An emergency measure is one thing; a bill with long-term implications passed as emergency legislation during the long-term "cold war" is another.

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FOOT-AND-MOUTH DISEASE IN CANADA

The "good neighbor policy" in this hemisphere is producing huge dividends in the present complete collaboration between Canadian and United States Government authorities, in their efforts to control the recent outbreak of foot-and-mouth disease. At the invitation of the Canadian government, a representative of the United States Bureau of Animal Industry assisted in the diagnosis of the disease and aided in the formulation of plans for its eradication. To date the cause has not been ascertained. The authorities are clinging to the hope that the present localization and apparent control of this disease will withstand the additional hazards that the spring weather will bring, with animals being turned out of winter confinement to range and semirange areas. Foot-and-mouth virus has a multiplicity of types; this outbreak is believed to be Type A.

Foot-and-mouth disease is enzootic in continental Europe, South America and elsewhere. In view of world conditions, which include food shortages and famine and, at the moment in this country, a lack of interest in establishing research facilities that are both accessible and safe, it might be well to review the changes that have occurred in New England and the rest of the country since New England was last visited by this disease in 1914.

The 1914 outbreak was the most widespread and costly that the country has known. Quarantine restrictions due to our methods of control, — which are still in effect, — were most drastic, even extending to the closing of the great Chicago stockyards. At that time "milk sheds" as they are known today did not exist. Per-capita consumption of milk by present standards was very low. This was then a meat-*exporting* nation. Interstate truck traffic in livestock was practically nonexistent. Tourist travel in the area was largely by rail. The public debt was low.

These 1914 conditions contrast vividly with the present. The disease itself, however, still retains all its ability to cause widespread damage to cloven-hoofed animals, and serious reduction to man's food supply. The slaughter method is still the most economical way of eradicating foot-and-mouth disease when it is discovered early. In Mexico, however, the disease got a head start and had spread widely through 16 states before effective measures were set up to stop it. Under those conditions, the Joint Mexico–United States Commission for the Eradication of Foot-and-Mouth Disease considered it necessary to use vaccine in addition to slaughter measures.

Much research is still to be done. Many persons will remember the Government's recent consideration of Prudence Island, off the Rhode Island coast, for such research, which was strongly opposed by some New England interests. *This should be reconsidered.* The present Canadian outbreak again emphasizes not only the need of great care in handling a disease of such extreme communicability but also the need for preparing for any emergency through

research. War in Europe would take away the only research centers available, in London, Denmark and Holland. In a widespread outbreak occurring today in this country, the economic disruption alone that would be brought about through quarantine would give rise to almost unbearable pressure in favor of temporizing. This could permanently fasten this disease burden to the nation and be a body blow to its agricultural production.

THE JAPAN MEDICAL ASSOCIATION

THE Japan Medical Association, with the associations of Thailand and Western Germany, was admitted to the World Medical Association in 1951. These additions brought the membership of that young but rapidly growing organization to over 40 national medical associations, all devoting part of their efforts and interest to mutual aid along such lines as the improvement of professional standards and professional ethics, the standardization of medical nomenclature, a universal pharmacopeia, medical education and studies in social security.

The original authorization for a Japan Medical Association goes back to a law passed in 1906 in the land of cherry blossoms, providing that "physicians may establish a medical association (which) may deliberate upon matters pertaining to medicine and health at the request of a government office or offices or make a recommendation thereon." Provincial associations were established, and in 1923 final permission was granted to set up a voluntary Japan Medical Association, "destined to be the precursor of the Japan Medical Association of today."

In February, 1942, a National Medical Treatment Law was promulgated with many regulations pertaining largely to the conduct of medicine in time of war. The formation of medical associations was made compulsory and their objects, to fit the needs of the times, became those of improving and promoting "guidance in medical treatment and health preservation" and co-operating "in furthering a national policy concerning development of physical strength." With the association in this state of utter captivity, the President became an appointee of the Cabinet on the recommendation of the Welfare Minister.

This compulsory association was dissolved in 1947, and a new voluntary association was established — in line with the efforts that were being made toward the democratization of Japan — into which was incorporated the Japanese Association of Medical Science. Even on its voluntary basis, the new association comprises some 55,000 members to serve a population of approximately 83,000,000 persons.

The main objectives of the Association are worthy ones, "to aim at elevation of medical ethics, development and diffusion of medical science and medical art, and improvement of public health in order to promote social welfare." Meanwhile the social-security program of the new Japan is being put under way as rapidly as economic conditions permit, with an advisory council of the Association seeking to guide it through the intricate steps that will lead to a plan of socialized medicine as acceptable as may be to all concerned.

Japan is engaged not only in a struggle back to normal living, whatever that may be, but in an attempt to adopt a democratic system of government — with the tendency for all democracies today to be cut on a socialistic pattern. Intelligent and industrious as the people may be who compose it, the question is whether a nation with so little experience in self-government can at once reap the benefits of democracy without becoming debased by the evils that tend to accompany it. However it turns out, the Japan Medical Association is in there trying to make the new Japan a going concern.

ZODIACUS MEDICUS

CORRESPONDENT Davidoff has raised a question in a communication published elsewhere in this issue of the *Journal* concerning the significance of the bull's head that has recently appeared at the bottom of various articles. How Dr. Davidoff guessed the sex of the animal in question is not divulged, since it has no ring in its nose and presents in many ways the sturdy outlines of a sacred cow of India.

In the note appended to Dr. Davidoff's letter the editors, somewhat but not greatly embarrassed, attempted an explanation of the presence of the animal involved. Far from implying any reflection on the quality or content of the article imme-

diately preceding it, the bull, representing neither "a grotesque blunder in language" or "a papal letter sealed with a bulla" (Webster's Collegiate Dictionary, Fifth Edition) refers only to that division of the zodiac that begins in April.

The reader who wonders what the zodiac has to do with it anyway need only be reminded that the first medical journal with which historians are acquainted was *Zodiacus Medicus*, published in Paris, in 1680. Unless a complete reader revolt takes place, *Taurus* will be succeeded — as it has already been preceded — by other zodiacal signs, in orderly sequence.

Cholera, in a few instances, has appeared at St. Joseph, Missouri. — Yellow fever is abating at Demerara. — Smallpox is still extending west and north. — Surgical instruments are manufactured in Boston and New York, equal to those of France or England.

Boston M. & S. J., *May 12, 1852*

MISCELLANY

JOURNAL OF PHYSICAL MEDICINE

Beginning with the issue of February, 1952, *Occupational Therapy and Rehabilitation*, now in its thirty-first volume, has become the *American Journal of Physical Medicine*. Published bimonthly by the Williams and Wilkins Company, of Baltimore, the new journal is under the editorship of H. D. Bouman, M.D., professor of physical medicine at the University of Wisconsin Medical School.

CORRESPONDENCE

REVOCATION OF LICENSE

To the Editor: This is to inform you that on April 10, 1952, the Board of Registration in Medicine revoked the registration of Dr. J. Leo Hanson, now of 1601 West Girard Avenue, Philadelphia.

ROBERT C. COCHRANE, M.D.

State House
Boston

DILEMMA

To the Editor: I have been puzzled by the significance of a recurring sketch of what appears to be a bull, appearing at the bottom of several articles in recent issues of the *Journal*. Could this be by way of whimsical editorial comment?

R. B. DAVIDOFF, M.D.

Boston, Massachusetts

NOTE: The little space-filling device to which Dr. Davidoff refers is the other kind of bull; only the front end is presented. In another sense this might represent the male analogue of the cartoonist Dahl's famous 5-spigot cow, Dilemma, suggesting the horns on which the editors so frequently find themselves.

Actually Taurus has put in his appearance in April as the month in which the particular sign of the zodiac with which he is associated becomes ascendant. If one looks back over recent issues of the *Journal* he will find Aquarius, the waterbearer, appearing in January; Pisces, as somewhat stylized fishes, in February; and Aries, the ram, in March. Whimsical, perhaps, these nevertheless seemed as good devices as any with which to relieve the monotony of those barren white spaces that occasionally occur at the end of articles. — ED.

BOOK REVIEWS

Psychoanalysis, Man and Society. By Paul Schilder, M.D., Ph.D. Arranged by Lauretta Bender, M.D. 8°, cloth, 382 pp. New York: W. W. Norton & Company, Incorporated, 1951. $4.00.

Realizing that the psychiatrist is concerned primarily with the individual and his conflicts, the author discusses in his book the need for psychiatry to view the person as a part of the community with its inherent problems.

In chapters on social and personal disorganization, social neurosis, alcoholism, crime and social organization, Dr. Schilder substantiates his fundamental thesis that in helping the badly adapted person by psychotherapy society gains a clearer approach to its own basic difficulties. The author points out that a disorganized society is one that neglects the rightful claims of the individual to an adequate development of his attitudes and emotions. This, then, provokes personal distortions in the individual who does not understand the threat and who counters with aggression and antisocial behavior. Such wrong attitudes thus developed are transmitted to children, are detrimental to their erotic and social development and, in turn, add to the disorganization of future society.

Interestingly enough, the writer believes that behavioral attitudes can be better elicited in group therapy than by the psychoanalytical interview, for in the group all the forces appear that are important in the structure of the community, and the isolation of the individual is broken when private ideologies become clarified and adjusted to the demands of the group.

Despite the scope of material, the author adheres to his initial concept of the role psychiatry should play in the interrelation between the individual and society. The book is well written and stimulating. The subject matter is pertinent and includes clear-cut illustrations from case histories. An adequate bibliography is included. The book is certainly a worth-while addition to progressive thought trends.

ELLEN F. BIRCHALL, M.D.

Bases of Human Behavior: A biologic approach to psychiatry. By Leon J. Saul, M.D. 8°, cloth, 150 pp., with 8 illustrations. Philadelphia: J. B. Lippincott Company, 1951. $4.00.

The author stresses the need of a concrete, concise textbook for first-year students in psychiatry; this book, with its biologic and physiologic approach, was written with this in mind.

Dr. Saul accepts many of the Freudian dynamic principles and stresses the fact that psychiatry must be taught as an exacting basic science, with a preliminary understanding that psychology has its roots in biologic and physiologic processes. The applications of this basic knowledge are the fundamentals necessary for psychodynamic interpretation. As a word of warning to young therapists, he says: "Psychodynamics is to psychological treatment what anatomy and physiology are to surgery. The psychotherapy of the personality is a form of psychological surgery, even more delicate and refined than neurosurgery."

He develops his thesis in the following manner: The human being must be regarded as a complex organism subject to powerful biologic motivations and also to powerful stimulation from environmental influences. When a conflict occurs, a state of stress is produced that affects the functioning of the organism. The stress, if mild, produces only minor alteration in function, but if it is prolonged, severe and even pathologic changes occur in the organ; this is demonstrated in the development of a peptic ulcer. When situations of stress occur, the body immediately reacts physiologically through the emergency mobilization mechanism. This is a normal temporary response until the adaptive or equilibratory forces are brought into play. Sometimes these fail, and chronic tension or anxiety states ensue, with chronic physi-

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ologic changes and resulting organic symptoms; these symptoms are the concern of psychosomatic medicine.

At times this conflictual material is not converted into physical symptoms or perceived as intellectual ideas as in the compulsion neurosis or in guilt the patient's impulses are not defended against by projection but exist as overt anxiety, causing him much suffering.

Emotional stress is one of the stimuli to which the body reacts as it does to other irritants and threats to its security, but it is amazing that the body reacts in a relatively limited number of ways to a relatively great variety of stimulants. Why one organ or system is affected rather than another is probably determined by constitutional factors and early environmental experiences.

The author elaborates at great length on the adaptive facilities of the human organism, using the work of Hans Selye but in a rather inclusive manner.

His handling of the id, ego and superego is essentially Freudian. He recognizes the ego as the mediator among the id, the superego and outer reality and states that if the ego does not have access to conflictual material it cannot mediate and there is a failure of adaptation.

He illustrates his theories by simple examples based on experimental work of Walter Cannon, Wolf and Wolff, Pavlov, Sherrington and, more recently, Selye. He hypothecates and enjoys philosophizing. Although much of his material is still in the research stage, he treats much of this conceptual material as though it were established facts. His opinion of maturity is exemplified by the following direct quotation: "Fully mature adults are strong, kind, friendly, constructive, responsible parents and citizens in contrast with the averaged warped, infantile personality, egotistic, lazy and filled with hate and destructiveness. The violence and cruelty in man is symptomatic of unhappiness and frustration. It threatens our very survival. It can be understood and dealt with just as effectively as has typhoid fever or smallpox." He states that a new type of disease has replaced smallpox and typhoid fever — that is, the neurosis and the other psychosomatic manifestations of mental conflicts. "High blood pressure is not only a disease of the individual — it is a disease of American life." "The causes are connected with our strivings for wealth. We have created false standards, have deprived ourselves of peace and leisure, and have lost the art of living wisely."

The book is readable and the material is well handled, but it shows the absence of original work, and it is doubtful that it will meet the author's expectations of an approved textbook.

ELOISE B. PETERSON, M.D.

Personality and Psychotherapy: An analysis in terms of learning, thinking, and culture. By John Dollard and Neal E. Miller. 8°, cloth, 488 pp., with 19 illustrations. New York: McGraw–Hill Book Company, Inc., 1950. $5.00. (McGraw–Hill Publications in Psychology.)

This book is an attempt to make a systematic analysis of neurosis and psychotherapy in terms of psychologic principles and the social conditions of learning. This is done not only for a better understanding of abnormal behavior but also because the authors believe that this method will lead to the discovery of factors that are important in normal behavior as well. Three great traditions are brought together —Freudian psychoanalysis, the experimental psychology of Pavlov and Thorndike and Hull and the modern social sciences of sociology and anthropology. First, the basic principles of learning that have been investigated in the psychologic laboratory are elaborated and discussed. The authors then apply these principles in explaining the normal use of the mind in solving emotional problems, the development of neurotic symptoms and the therapeutic process. Anxiety and conflict, with other psychoanalytic concepts, are discussed in detail within the authors' theoretical framework, as well as some of the conditions necessary for successful psychotherapy.

Professors Dollard and Miller have a clear, precise, but deceptively simple style of writing. A reader unfamiliar with their theoretical formulation of the learning process will do well to read the chapters stating the basic principles with great care. These chapters contain the definitions and postulates necessary to an understanding of the later analysis of the neuroses and psychotherapy.

This book is a well-written, logical and scholarly analysis of the development of personality. The theoretical formulations are bolstered whenever possible by psychologic, sociologic and anthropologic data. The authors carefully refrain from excessive speculation but draw conclusions from current research that point toward new problems to be investigated. Although it is not intended as a practical handbook for psychotherapists, it does provide a frame of reference that many practicing psychotherapists will find interesting. This book successfully integrates many of the Freudian conceptions of personality with those based on scientific psychology; it describes their operation within the framework of the social situation.

ELIZABETH L. WESLEY, PH.D.

The Quantitation of Mixtures of Hemoglobin Derivatives by Photoelectric Spectrophotometry. By Francis T. Hunter, M.D. 8°, cloth, 226 pp., with 42 charts. Springfield, Illinois: Charles C Thomas, 1951. $8.50.

Dr. Hunter has rendered a great service to the clinical technician by assembling a useful array of methods for the determination of the various hemoglobin components. There is no doubt that many of the spectrophotometric technics that he has described will become standard laboratory procedures. The primary advantage of these optical technics over the older gasometric procedures lies in their great speed and simplicity and the minute size of the sample required. A high degree of precision is possible when the tests are properly performed. Technics are described for the spectrophotometric determination of such substances as oxyhemoglobin, hemochromogen, carbon-monoxide hemoglobin and serum and bile pigments. Although the principles employed in these determinations are sound, it must be borne in mind that the validity of any spectrophotometric technic ultimately rests on other methods. So, for example, the spectrophotometric determination of the oxygen capacity rests on an actual gasometric measurement. It is true, I think, that spectrophotometric analyses, on certain occasions, may be more difficult to interpret than gasometric technics because they do not directly determine the quantities involved.

Although the graphs presented by Dr. Hunter are of undoubted utility, it is to be regretted that certain of the data do not appear to be internally consistent. For example, the absorption spectra of two concentrations of reduced hemoglobin do not appear to be equivalent; when plotted on a logarithmic basis they have different shapes.

Dr. Hunter presents an extended discussion of the mathematical theory of the construction of the nomograms and alignment charts that he uses, thereby making it possible to devise one's own charts for a particular set of conditions. This will prove to be a most useful part of the book, although it demands considerably more from the reader than does the procedural part.

In summary, this book brings to the clinical laboratory a host of technics that are extremely valuable because they can be used rapidly and easily and can be made very precise. I recommend the use of such technics to all those who need to make quantitative clinical determinations of hemoglobin and its various derivatives.

AUSTEN RIGGS, M.D.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Children's Radiographic Technic. By Forrest E. Shurtleff, R.T., Children's Medical Center, Boston. 4°, cloth, 80 pp., with 32 illustrations and 41 tables. Philadelphia: Lea and Febiger, 1951. $3.75.

This small manual describes in detail the radiologic methods used in the examination of small children at the Children's Medical Center in Boston. The material is divided into four parts: equipment and accessories; children's radiographic positions; special radiographic procedure; and children's

technic. This last section was compiled from an experience of over eight years with a 500-MA machine; during this period more than 200,000 exposures were made, including all varieties of radiographic procedures. The tables are arranged alphabetically by regions and the various technics have been segregated by age groups. The printing is well done, with a large type that is easy to read, and there is a good index. The manual should be in all collections on pediatrics and on radiology.

Food and You. By Edmund S. Nasset, M. S., Ph.D., professor of physiology, University of Rochester School of Medicine and Dentistry. 8°, cloth, 92 pp. Springfield, Illinois: Charles C Thomas, 1951. $3.00.

In this new type of book on dietetics Professor Nasset discusses the general principles of the subject. The book contains no detailed dietetic charts. It was written especially by the author for his two daughters and could be read with profit by all persons. The text is written in a clear and simple style. There is a good index, and the book is well printed.

Disease in Infancy and Childhood. By Richard W. B. Ellis, O.B.E., M.A., M.D., F.R.C.P., professor of child life and health, University of Edinburgh, and physician, Royal Hospital for Sick Children, Edinburgh. 8°, cloth, 695 pp., with 300 illustrations. Baltimore: The Williams and Wilkins Company, 1951.

This new textbook on pediatrics covers the whole field, from history-taking to procedures and therapy. A list of references is appended to each of the chapters, and there is a good index. The printing was done in Great Britain on a heavy-coated paper. The book should be in special collections on pediatrics.

Low-Sodium Diet: A manual for the patient. By Thurman B. Rice, A.M., M.D., professor of public health, Indiana University School of Medicine, Indianapolis. 8°, cloth, 103 pp. Philadelphia: Lea and Febiger, 1951. $2.75.

In this popular manual Dr. Rice tells how to prepare "salt-free" foods and provides a helpful guide for all persons who must avoid salt in the foods they eat or prepare for others. Foods lists rated by the content of natural sodium, food charts and sample diets are included in the text. There is an index, and the publishing is excellent.

Clinical Hematology. By Maxwell M. Wintrobe, M.D., Ph.D., professor of medicine and director, Laboratory for the Study of Hereditary and Metabolic Disorders, University of Utah College of Medicine. Third edition. 8°, cloth, 1048 pp., with 220 illustrations and 17 plates. Philadelphia: Lea and Febiger, 1951. $12.50.

Dr. Wintrobe has thoroughly revised his standard work to bring it up to date. Much of the text has been completely rewritten, and new material has been added on cytochemistry, splenic puncture and the role of heredity in hemopoietic disorders. The use of the newer treatments with vitamins, hormones and chemotherapeutic agents is considered. The text has been enlarged by 180 pages. Lists of references are appended to the various chapters, and there is a comprehensive index. The publishing is excellent, and the book should be in all medical libraries and in the collections of hematologists.

Die Nervenkrankheiten. By Prof. Dr. Georges Schaltenbrand, Ordinarius für Nervenheilkunde und innere Medizin und Direktor der Neurologischen Universitäts-Klinik, Würzburg. 8°, cloth, 880 pp., with 539 illustrations. Stuttgart: Georg Thieme, 1951. Ganzleinen DM 87. Distributed by Grune and Stratton, Incorporated, New York. (Lehrbuch der Neurologie: Part 1.)

This comprehensive treatise on diseases of the nerves forms Part 1 of a projected *Lehrbuch der Neurologie*, by Professor Schaltenbrand. The diseases of the brain and meninges, the central nervous system and the nerves are thoroughly covered. The concluding chapter discusses the virus diseases of the nervous system. There is a bibliography of 69 pages and a good index. The publishing is excellent in every way and the book should be in all medical libraries.

Atlas der pathologischen Anatomie: Eine Sammlung typischer Krankheitsbilder der menschlichen Organe. By Dr. med., Dr. med. vet. h.c. Robert Rössle, and Dr. med. Kurt Apitz. 4°, cloth, 298 illustrations. Stuttgart: Georg Thieme, 1951. Ganzleinen DM 87. Distributed by Grune and Stratton, Incorporated, New York.

This new atlas of pathologic anatomy presents a collection of typical pictures of diseases of the various organs of man. The color work is excellent, approaching if not equaling the prewar standards. The material consists of plates with descriptive text, arranged according to the organs and systems of the body. The publishing is excellent and there is a good index; the book should be in all collections on the subject.

Deutsch-englisches, english-deutsches Wörterbuch für Ärzte. By Prof. med., Dr. phil, Dr. med. dent. Fritz Lejeune. Vol. 1, German-English. 16°, cloth, 1349 pp. Stuttgart: Georg Thieme, 1951. Ganzleinen DM 24.

This new German medical dictionary is comprehensive in scope and lists a great number of medical and related words, including some in the vernacular, for the use of all persons interested in reading medical literature. Volume 2, now in the process of compilation, will constitute the English-German part. The volume is small and easy to handle. It should be in all medical libraries and available to all persons interested in German medical literature.

Bacterial and Virus Diseases: Antisera, toxoids, vaccines and tuberculins in prophylaxis and treatment. By H. J. Parish, M.D., F.R.C.P.E., D.P.H., clinical research director, Wellcome Foundation Ltd. Second edition. 12°, cloth, 204 pp., with 20 plates. Baltimore: The Williams and Wilkins Company, 1951. $2.50.

In this new edition of his monograph, first published in 1948, Dr. Parish has thoroughly revised his text to bring it up to date. The chapter on antivenoms has been completely rewritten. A historical chronology has been appended to the text, and there is a good index. The excellent printing was done in Great Britain.

The Organization of Bones. By P. Lacroix, professor in the Faculty of Medicine, University of Louvain. Translated from the amended French edition by Stewart Gilder, B.Sc., M.B. 8°, cloth, 235 pp., with 87 illustrations. Philadelphia: The Blakiston Company, 1951. $6.00.

This valuable monograph, originally written in French, has now been made available to English physicians. A long bibliography is appended to the text, and there is a good index. The text is well printed, with a good type, and the printing was done in Great Britain. The book should be in all collections on osteology and on orthopedics.

Ophthalmology. By Arno E. Town, M.D., professor of ophthalmology, Jefferson Medical College of Philadelphia, and eleven contributors. 8°, cloth, 511 pp., with 208 illustrations and 4 plates in color. Philadelphia: Lea & Febiger, 1951. $10.00.

In this new book on ophthalmology the authors have endeavored to present a concise treatise for the undergraduate student and the general practitioner. Special emphasis has been placed on the use of the ophthalmoscope and the interpretation of the fundus picture. Lists of selected references are appended to the various chapters, and there is a good index. The illustrations are excellent. The book should be in all collections on the subject.

A Textbook of Medicine. Edited by E. Noble Chamberlain, M.D., M.Sc., F.R.C.P., senior lecturer in medicine, University of Liverpool, senior physician, Royal Southern Hospital, Liverpool, and physician in charge, Medical Unit, Sefton General Hospital, Liverpool. 8°, cloth, 962 pp., with 266 illustrations. Baltimore: The Williams and Wilkins Company, 1951. $10.00.

This new textbook of medicine is the joint work of 17 British physicians, all specialists in their fields. The book has been written primarily for the student of medicine and the approach is clinical, with emphasis on methods of examination. The excellent printing was done in Great Britain but, unfortunately, on coated paper. The text is concluded with a comprehensive index.

NOTICES

SOUTH END MEDICAL CLUB

The next luncheon meeting of the South End Medical Club will be held at the headquarters of the Boston Tuberculosis Association, 554 Columbus Avenue, Boston, on Tuesday, May 13.

The speaker will be Dr. Joseph H. Phillips, associate visiting surgeon, Free Hospital for Women, and senior visiting surgeon, Malden Hospital. His subject will be: "Problems of Male and Female Infertility." All physicians are invited to attend.

THE NEW ENGLAND RHEUMATISM SOCIETY

The Rheumatism Society will hold its annual meeting on May 23 at 8 p.m. in Farnsworth Lecture Hall of the New England Center Hospital. The program will be announced later.

NEW ENGLAND HEALTH INSTITUTE

The eighteenth New England Health Institute will be held at the University of Connecticut, Storrs, Connecticut, June 18-20.

Further information may be obtained from Dr. Alfred L. Burgdorf, State Department of Health, 165 Capitol Avenue, Hartford 15, Connecticut.

AMERICAN COLLEGE OF CARDIOLOGY

The first annual convention of the American College of Cardiology will be held in the Hotel Statler, New York City, June 6 and 7. Four scientific sessions will comprise a symposium on treatment of the cardiac patient.

Further information may be obtained from Dr. Philip Reichert, 480 Park Avenue, New York 22, N. Y.

WASHINGTONIAN HOSPITAL INSTITUTE ON ALCOHOLISM

An afternoon and evening institute on alcoholism will be held at the Washingtonian Hospital on May 20. The afternoon session will be held from 2:00 to 4:00 p.m., the evening session from 7:30 to 9:00 p.m. Recent films on alcoholism will be presented. There will be no registration fee. All physicians are invited to attend.

BOSTON CITY HOSPITAL HOUSE OFFICERS' ASSOCIATION

The Boston City Hospital House Officers' Association announces that the address by Dr. Robert P. Grant on "An Introduction to Vector Electrocardiography" has been postponed from May 6 to June 5.

NEW ENGLAND VETERANS ADMINISTRATION SURGICAL SOCIETY

The third annual meeting of the New England Veterans Administration Surgical Society will be held in the third-floor auditorium of the Veterans Administration Hospital, West Roxbury, on May 23 at 10 a.m. Dr. Richard Warren will preside.

All physicians are invited to attend.

CDA MEDICAL DIRECTORS

The Council on National Emergency Medical Service of the American Medical Association announces that the Federal Civil Defense Administration's regional offices are authorized to employ full-time physicians to direct medical problems arising within the 9 geographical areas. The positions pay $10,800. Further information may be obtained from the secretary of the Council, 535 North Dearborn Street, Chicago 10, Illinois.

SOCIETY MEETINGS AND CONFERENCES

MAY 8–10. American Neurological Association. Page 559, issue of April 3.

MAY 9–JUNE 3. Boston City Hospital House Officers' Association. Page 634, issue of April 17.

MAY 10. Boston Dispensary Proctologic Session. Page 433, issue of March 13.

MAY 10 AND 11. American Electroencephalographic Society. Page 390, issue of March 6.

MAY 10–31. Springfield Hospital. Page 635, issue of April 17.

MAY 11–17. Pan-American Convention of Gastroenterology. Page 434, issue of March 13.

MAY 12. New England Cardiovascular Society. Page 720, issue of May 1.

MAY 13. South End Medical Club. Notice above.

MAY 13. Springfield Academy of Medicine. Page 635, issue of April 17.

MAY 13. New England Society of Anesthesiologists. Page 635, issue of April 17.

MAY 13 AND 20. Children's Cancer Research Foundation. Page 676, issue of April 24.

MAY 15. New England Diabetes Association. Page 720, issue of May 1.

MAY 15–17. American College of Surgeons. Page 596, issue of April 10.

MAY 16. New England Pediatric Society. Page 676, issue of April 24.

MAY 19–22. Massachusetts Medical Society. Hotel Statler, Boston. Pages 716-720, issue of May 1.

MAY 19–23. Courses in Laboratory Diagnosis of Tuberculosis. Page 354, issue of February 28.

MAY 20. Washingtonian Hospital Institute on Alcoholism. Notice above.

MAY 21 AND 22. Venereal-Disease Seminar. Page 559, issue of April 3.

MAY 22–24. American Academy of Pediatrics. Page 522, issue of March 27.

MAY 23. The New England Rheumatism Society. Notice above.

MAY 23. New England Veterans Administration Surgical Society. Notice above.

MAY 24. Annual Meeting. Massachusetts Association of Medical Technologists, Inc.

MAY 26–28. Minnesota State Medical Association. Annual Meeting. Page 316, issue of February 21.

MAY 26–29. National Tuberculosis Association. Copley Plaza and Statler hotels, Boston.

MAY 29–31. American Academy of Dental Medicine. Page 476, issue of March 20.

JUNE 5. Boston City Hospital House Officers' Association. Notice above.

JUNE 5. New York Society for Circulatory Diseases. Page 676, issue of April 24.

JUNE 5–8. American College of Chest Physicians. Page 280, issue of February 14.

JUNE 6 AND 7. American College of Cardiology. Notice above.

JUNE 7 AND 8. Society for Investigative Dermatology, Inc. Page 676, issue of April 24.

JUNE 18–20. Massachusetts Public Health Conference. Amherst.

JUNE 18–20. New England Health Institute. Notice above.

JUNE 19–21. American Association of Genito-Urinary Surgeons. Page 434, issue of March 13.

JUNE 22–26. American Society of Medical Technologists. Twentieth Annual Convention. Portland, Oregon.

JULY. Commonwealth and Empire Health and Tuberculosis Conference. Page 792, issue of November 15.

JULY 7–11. International Congress of Dietetics. Page 434, issue of March 13.

JULY 7–12. International Diabetes Federation. Page 316, issue of February 21.

JULY 8–11. Thirteenth British Congress of Obstetrics and Gynecology. Page 916, issue of December 6.

JULY 14–19. International Congress of Physical Medicine. Page 998, issue of June 28.

JULY 24–26. Conference on Aging. Page 559, issue of April 3.

AUGUST 25–29. American Congress of Physical Medicine. Page 476, issue of March 20.

AUGUST 31–SEPTEMBER 6. Interamerican Congress of Cardiology. Page 422, issue of March 27.

SEPTEMBER 7–9. Combined session of the New Hampshire and Vermont State Medical Societies. Mount Washington Hotel, Bretton Woods, New Hampshire.

OCTOBER 28–30. New England Postgraduate Assembly. Hotel Statler, Boston.

OCTOBER 29. New England Obstetrical and Gynecological Society. Annual Meeting. Hotel Somerset, Boston.

NOVEMBER 3–7 AND 10–21. Courses in Laboratory Diagnosis of Tuberculosis. Page 354, issue of February 28.

JULY, 1953. International Congress on Medical Librarianship. Page 316, issue of February 21.

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, MAY 15

THURSDAY, MAY 15

8:30–10:00 a.m. Fracture Conference. Boston City Hospital.

*9:00–10:00 a.m. Grand Rounds. Robert Breck Brigham Hospital.

12:00 m.–1:00 p.m. Weekly guest speaker. Dr. George Van S. Smith. Antitoxic Action of Penicillin.

4:00 p.m. Department of Bacteriology and Immunology. Synthesis and Biological Properties of Polyamino Acids. Dr. E. Katchalski. Amphitheatre D, Harvard Medical School.

(Notices concluded on page xv)